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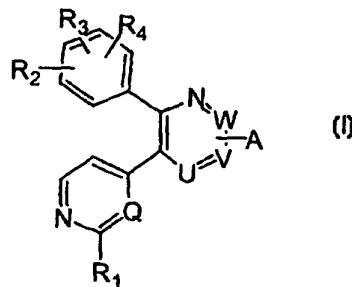
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(54) Title: COMPOUNDS HAVING CYTOKINE INHIBITORY ACTIVITY



(57) Abstract

There are disclosed compounds of formula (I) and pharmaceutically acceptable salts thereof which exhibit utility for the treatment of cytokine mediated diseases such as arthritis.

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TITLE OF THE INVENTION**COMPOUNDS HAVING CYTOKINE INHIBITORY ACTIVITY****BACKGROUND OF THE INVENTION**

5 The present invention relates to substituted heterocyclic compounds which have cytokine inhibitory activity. Cytokine mediated diseases and cytokine inhibition, suppression and antagonism are used in the context of diseases or conditions in which excessive or unregulated production or activity of one or 10 more cytokines occurs. Examples of cytokines which are effected typically include Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8) and Tumor Necrosis Factor (TNF).

15 Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are produced by a variety of cells which are involved in immunoregulation and other physiological conditions.

17 There are many disease states in which IL-1 is implicated. Examples are rheumatoid arthritis, osteoarthritis, endotoxemia, toxic shock syndrome, acute and chronic inflammatory diseases, such as the inflammatory reaction 20 induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis. Recent 25 evidence also links IL-1 activity to diabetes.

27 Interleukin-1 has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions. Dinarello *et al.*, *Rev. Infect. Disease*, 6, 51 (1984). The known biological 30 activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

Excessive or unregulated tumor necrosis factor (TNF) production or activity has been implicated in mediating or

exacerbating rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral 5 malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft v. host rejection, allograft rejections, fever and myalgia due to infection, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome 10 (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis.

Monokines, such as TNF, have also been shown to activate HIV replication in monocytes and/or macrophages [See Poli, *et al.*, *Proc. Natl. Acad. Sci.*, 87:782-784 (1990)], therefore, 15 inhibition of monokine production or activity aids in limiting HIV progression. TNF has been implicated in various roles with other viral infections, such as the cytomegalovirus (CMV), influenza virus and the herpes virus.

Interleukin-6 (IL-6) is a cytokine effecting the immune 20 system and hematopoiesis. It is produced by several mammalian cell types in response to agents such as IL-1, and is correlated with disease states such as angiofollicular lymphoid hyperplasia.

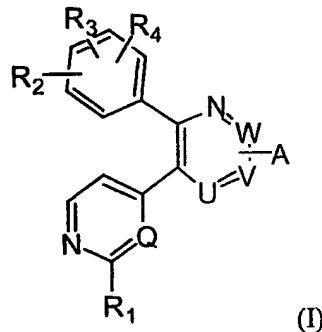
Interleukin-8 (IL-8) is a chemotactic factor first 25 identified and characterized in 1987. Many different names have been applied to IL-8, such as neutrophil attractant/activation protein-1 (NAP-1), monocyte derived neutrophil chemotactic factor (MDNCF), 30 neutrophil activating factor (NAF), and T-cell lymphocyte chemotactic factor. Like IL-1, IL-8 is produced by several cell types, including mononuclear cells, fibroblasts, endothelial cells and ketainocytes. Its production is induced by IL-1, TNF and by

lipopolysaccharide (LPS). IL-8 stimulates a number of cellular functions *in vitro*. It is a chemoattractant for neutrophils, T-lymphocytes and basophils. It induces histamine release from basophils. It causes lysozymal enzyme release and respiratory 5 burst from neutrophils, and it has been shown to increase the surface expression of Mac-1 (CD 11b/CD 18) on neutrophils without *de novo* protein synthesis.

There remains a need for compounds which are useful in treating cytokine mediated diseases, and as such, inhibit, 10 suppress or antagonize the production or activity of cytokines such as IL-1, IL-6, IL-8 and TNF.

SUMMARY OF THE INVENTION

The present invention relates to compound I of the 15 formula



wherein:

A is 20 hydrogen, or a saturated heterocyclic group selected from pyrrolidine, morpholine and piperidine; with the nitrogen atom or atoms optionally substituted with hydrogen or C1-C6 alkyl;

Q, U, V and W are independently CH or N; 25
R¹ is hydrogen or NH(C1-C6 alkyl) aryl;

5 **R², R³ and R⁴ independently represent a member selected from the group consisting of: hydrogen; halo; hydroxy; CF₃; NH₂; NO₂, C₁-C₆ alkyl, substituted C₁-C₆ alkyl; C₁-C₆ alkoxy, substituted C₁-C₆ alkoxy; C₃-C₈ cycloalkyl, substituted C₃-C₈ cycloalkyl; aryl or substituted aryl;**

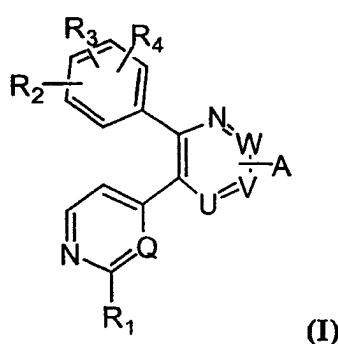
10 **or a pharmaceutically acceptable addition salt and/or hydrate thereof, or where applicable, a geometric or optical isomer or racemic mixture thereof.**

15 A pharmaceutical composition is also included in the invention described herein, which is comprised of a compound of formula I as defined above in combination with a pharmaceutically acceptable carrier.

20 Also included in the invention is a method of treating a cytokine mediated disease in a mammal, comprising administering to a mammalian patient in need of such treatment an amount of a compound of formula I which is effective for treating said cytokine mediated disease.

DETAILED DESCRIPTION OF THE INVENTION

25 The present invention relates to compound I of the formula



wherein:

A is hydrogen, or a saturated heterocyclic group selected from pyrrolidine, morpholine and piperidine; with the nitrogen atom or atoms optionally substituted with
5 hydrogen or C₁-C₆ alkyl;

Q, U, V and W are independently CH or N;

R¹ is hydrogen or NH(C₁-C₆ alkyl) aryl;

10 R², R³ and R⁴ independently represent a member selected from the group consisting of: hydrogen; halo; hydroxy; CF₃; NH₂; NO₂; C₁-C₆ alkyl, substituted C₁-C₆ alkyl; C₁-C₆ alkoxy, substituted C₁-C₆ alkoxy; C₃-C₈ cycloalkyl,
15 substituted C₃-C₈ cycloalkyl; aryl or substituted aryl;

or a pharmaceutically acceptable addition salt and/or hydrate thereof, or where applicable, a geometric or optical isomer or racemic mixture thereof.

20 In a preferred embodiment, there are disclosed compounds of formula I wherein

A is hydrogen, or piperidine with the nitrogen atom substituted with hydrogen or C₁-C₆ alkyl;

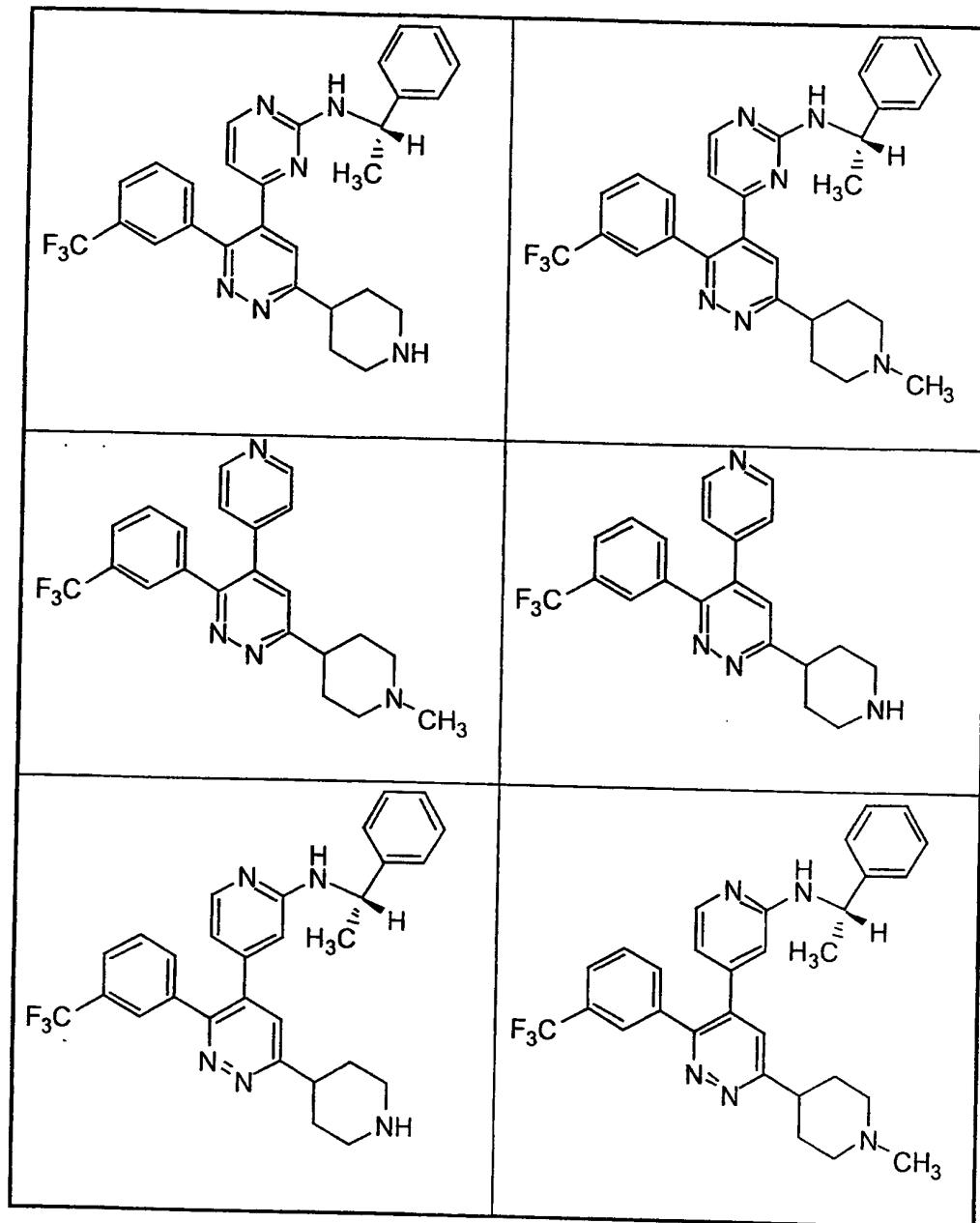
25 Q, U and W are independently CH or N;

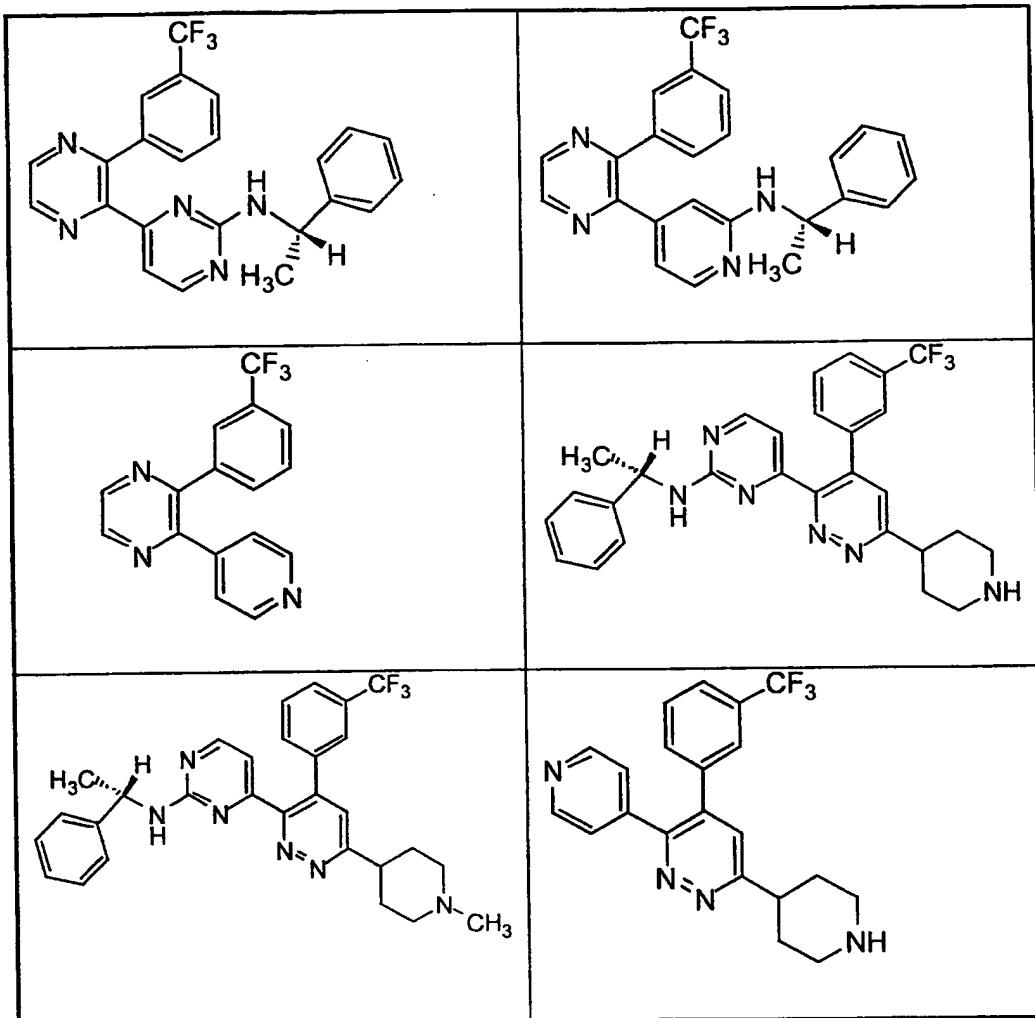
R¹ is hydrogen or NHCH(CH₃) phenyl;

30 R², R³ and R⁴ are independently hydrogen or CF₃;

or a pharmaceutically acceptable addition salt and/or hydrate thereof, or where applicable, a geometric or optical isomer or racemic mixture thereof.

Representative species falling within the present invention include the following:





Unless otherwise stated or indicated, the following definitions shall apply throughout the specification and claims.

The term "alkyl" refers to a monovalent alkane

- 5 (hydrocarbon) derived radical containing from 1 to 15 carbon atoms unless otherwise defined. It may be straight or branched, and when of sufficient size, e.g., C3-15 may be cyclic. Preferred straight or branched alkyl groups include methyl, ethyl, propyl,
- 10 isopropyl, butyl and t-butyl. Preferred cycloalkyl groups include cyclopropyl, cyclopentyl and cyclohexyl.

Alkyl also includes an alkyl group substituted with a cycloalkyl group, such as cyclopropylmethyl. Alkyl also includes a straight or branched alkyl group

The alkylene and monovalent alkyl portion(s) of the
5 alkyl group can be attached at any available point of attachment to the cycloalkylene portion.

When substituted alkyl is present, this refers to a straight, branched or cyclic alkyl group as defined above, substituted with 1-3 groups as defined with respect to each
10 variable.

The term "aryl" refers to aromatic rings e.g., phenyl, substituted phenyl and like groups as well as rings which are fused, e.g., naphthyl and the like. Aryl thus contains at least one ring having at least 6 atoms, with up to two such
15 rings being present, containing up to 10 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms. The preferred aryl groups are phenyl and naphthyl. Aryl groups may likewise be substituted as defined below. Preferred substituted aryls include phenyl or naphthyl
20 substituted with one or two groups.

The terms "heterocycloalkyl" and "heterocyclyl" refer to a cycloalkyl group (nonaromatic) in which one of the carbon atoms in the ring is replaced by a heteroatom selected from O, S(O)y or N, and in which up to three additional carbon atoms may
25 be replaced by said heteroatoms. When three heteroatoms are present in the heterocycle, they are not all linked together.

Examples of heterocycls are piperidinyl, morpholinyl, azetidinyl, pyrrolidinyl, tetrahydrofuranyl, imidazolinyl, piperazinyl, pyrrolidin-2-one, piperidin-2-one and the
30 like.

The term "halogen" or "halo" is intended to include fluorine, chlorine, bromine and iodine.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the

specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

In addition, it is well known to those skilled in the art
5 that many of the foregoing heterocyclic groups can exist in more than one tautomeric form. It is intended that all such tautomers be included within the ambit of this invention.

The optical isomeric forms, that is mixtures of enantiomers, e.g., racemates, or diastereomers as well as
10 individual enantiomers or diastereomers of the instant compound are included. These individual enantiomers are commonly designated according to the optical rotation they effect by the symbols (+) and (-), (L) and (D), (1) and (d) or combinations thereof. These isomers may also be designated according to their
15 absolute spatial configuration by (S) and (R), which stands for sinister and rectus, respectively.

The individual optical isomers may be prepared using conventional resolution procedures, e.g., treatment with an appropriate optically active acid, separating the diastereomers
20 and then recovering the desired isomer. In addition, the individual optical isomers may be prepared by asymmetric synthesis.

Additionally, a given chemical formula or name shall encompass pharmaceutically acceptable addition salts thereof
25 and solvates thereof, such as hydrates.

The compounds of the present invention, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable addition salts for purposes of stability, convenience of crystallization, increased
30 solubility and other desirable properties.

The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" is intended to include all acceptable salts. Examples of acid salts are hydrochloric,

nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic, methane sulfonic and the like which can be used as a dosage form for modifying the solubility or hydrolysis characteristics or can be used in

5 sustained release or prodrug formulations. Depending on the particular functionality of the compound of the present invention, pharmaceutically acceptable salts of the compounds of this invention include those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc, and

10 from bases such as ammonia, ethylenediamine, N-methyl-glutamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, and tetramethyl-

15 ammonium hydroxide. These salts may be prepared by standard procedures, e.g. by reacting a free acid with a suitable organic or inorganic base, or alternatively by reacting a free base with a suitable organic or inorganic acid.

Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed, e.g. methyl, ethyl, butyl, acetate, maleate, pivaloyloxymethyl, and the like, and those esters known in the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

25 The compounds of the present invention may have chiral centers other than those centers whose stereochemistry is depicted in formula I, and therefore may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers, with all such isomeric forms being included in

30 the present invention as well as mixtures thereof. Furthermore, some of the crystalline forms for compounds of the present invention may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds of the instant invention

may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of this invention.

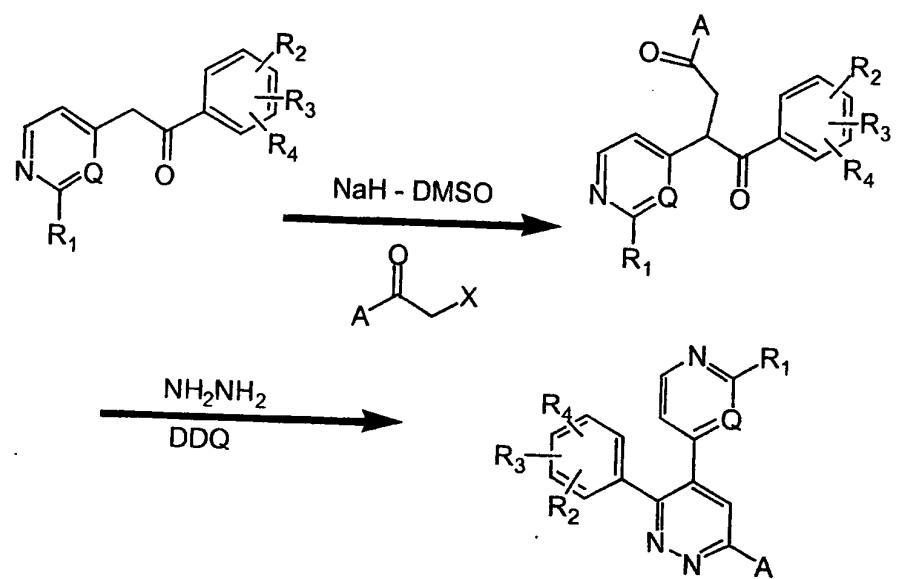
The term "TNF mediated disease or disease state"

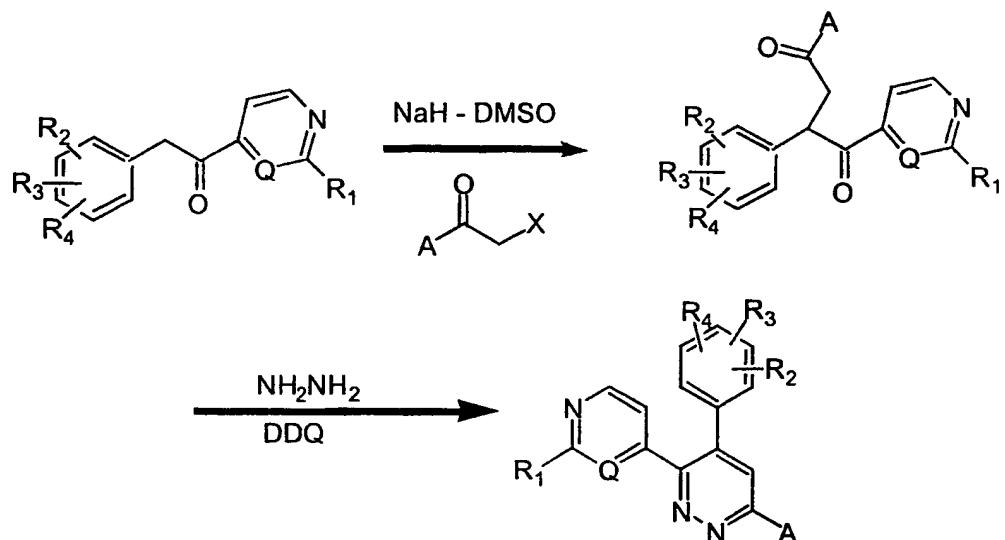
5 refers to disease states in which TNF plays a role, either by production or increased activity levels of TNF itself, or by causing another monokine to be released, such as but not limited to IL-1 or IL-6. A disease state in which IL-1, for instance is a major component, 10 and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF.

The term "cytokine" as used herein means any secreted polypeptide that affects the functions of cells and is a molecule 15 which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines regardless of which cells produce them. Examples of cytokines include, but are not limited to, Interleukin-1 20 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF- α) and Tumor Necrosis Factor-beta (TNF- β).

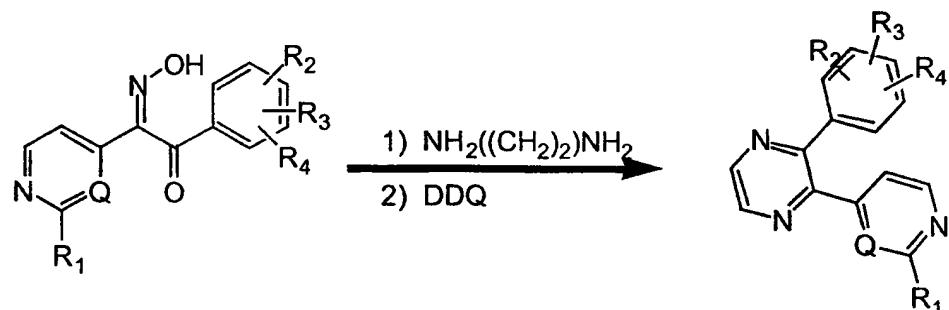
By the term "cytokine interfering or cytokine suppressive amount" is meant an effective amount of a compound of formula I which will cause a decrease in the *in vivo* activity or 25 level of the cytokine to normal or sub-normal levels, when given to the patient for the prophylaxis or therapeutic treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated cytokine production or activity.

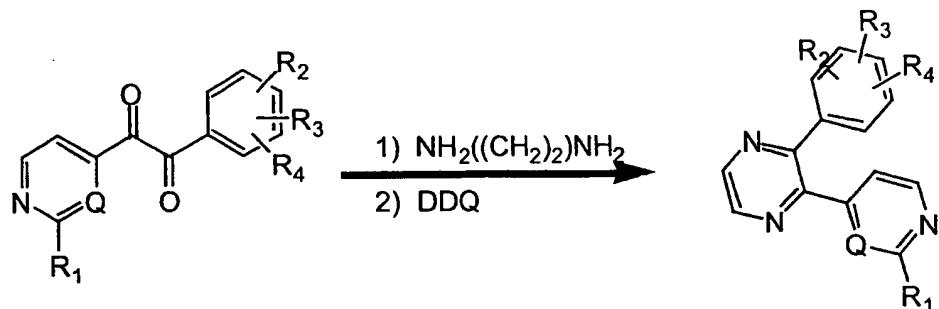
30 The compounds of the invention are prepared by the following reaction schemes. All substituents are as defined above unless indicated otherwise.

Scheme I

Scheme II**Preparation of Pyrazines**

5

Scheme I

Scheme II

The compounds of formula 1 can be used in the prophylactic or therapeutic treatment of disease states in

5 mammals which are exacerbated or caused by excessive or unregulated cytokines, e.g., IL-1, IL-6, IL-8 or TNF.

Because the compounds of formula I inhibit cytokines, the compounds are useful for treating diseases in which cytokine presence or activity is implicated, such as rheumatoid arthritis, 10 rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions.

The compounds of formula I are useful to treat disease states mediated by excessive or unregulated TNF production or activity. Such diseases include, but are not limited to sepsis, 15 septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, such as osteoporosis, reperfusion injury, graft v. host rejection, allograft rejection, 20 fever, myalgia due to infection, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDs related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, AIDS and other viral infections, such as 25 cytomegalovirus (CMV), influenza virus, and the herpes family of viruses such as Herpes Zoster or Simplex I and II.

The compounds of formula I are also useful topically in

the treatment of inflammation such as in the treatment of rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis,

5 gouty arthritis and

other arthritic conditions; inflamed joints, eczema, psoriasis or other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

10 The compounds of formula I are also useful in treating diseases characterized by excessive IL-8 activity. These disease states include psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis.

15 The invention thus includes a method of treating psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis, in a mammal in need of such treatment, which comprises administering to said mammal a

20 compound of formula I in an amount which is effective for treating said disease or condition.

When administered to a patient for the treatment of a disease in which a cytokine or cytokines are implicated, the dosage used can be varied within wide limits, depending upon the

25 type of disease, the age and general condition of the patient, the particular compound administered, the presence or level of toxicity or adverse effects experienced with the drug and other factors. A representative example of a suitable dosage range is from as low as about 0.01 mg/kg to as high as about 100 mg/kg.

30 However, the dosage administered is generally left to the discretion of the physician.

The methods of treatment can be carried out by delivering the compound of formula I parenterally. The term 'parenteral' as used herein includes intravenous, intramuscular,

or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. The instant invention can also be carried out by delivering the compound of formula I subcutaneously, 5 intranasally, intrarectally, transdermally or intravaginally.

The compounds of formula I may also be administered by inhalation. By 'inhalation' is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose 10 inhaler, may be prepared by convention techniques.

The invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier. The compounds of formula I may also be included in pharmaceutical compositions in 15 combination with a second therapeutically active compound.

The pharmaceutical carrier employed may be, for example, either a solid, liquid or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Examples 20 of liquid carriers are syrup, peanut oil, olive oil, water and the like. Examples of gaseous carriers include carbon dioxide and nitrogen.

Similarly, the carrier or diluent may include time 25 delay material well known in the art, such as glyceryl monostearate or glyceryl distearate, alone or with a wax.

A wide variety of pharmaceutical dosage forms can be employed. If a solid dosage is used for oral administration, the preparation can be in the form of a tablet, hard gelatin capsule, troche or 30 lozenge. The amount of solid carrier will vary widely, but generally will be from about 0.025 mg to about 1 g. When a liquid dosage form is desired for oral administration, the preparation is typically in the form of a syrup, emulsion, soft gelatin capsule, suspension or solution. When a parenteral dosage form is to be

employed, the drug may be in solid or liquid form, and may be formulated for administration directly or may be suitable for reconstitution.

Topical dosage forms are also included. Examples of 5 topical dosage forms are solids, liquids and semi-solids. Solids would include dusting powders, poultices and the like. Liquids include solutions, suspensions and emulsions. Semi-solids include creams, ointments, gels and the like.

The amount of a compound of formula I used topically 10 will, of course, vary with the compound chosen, the nature and severity of the condition, and can be varied in accordance with the discretion of the physician. A representative, topical, dose of a compound of formula I is from as low as about 0.01 mg to as high as about 2.0 g, administered one to four, preferably one to two 15 times daily.

The active ingredient may comprise, for topical administration, from about 0.001% to about 10% w/w.

Drops according to the present invention may comprise sterile or non-sterile aqueous or oil solutions or 20 suspensions, and may be prepared by dissolving the active ingredient in a suitable aqueous solution, optionally including a bactericidal and/or fungicidal agent and/or any other suitable preservative, and optionally including a surface active agent. The resulting 25 solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container aseptically. Examples of 30 bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise

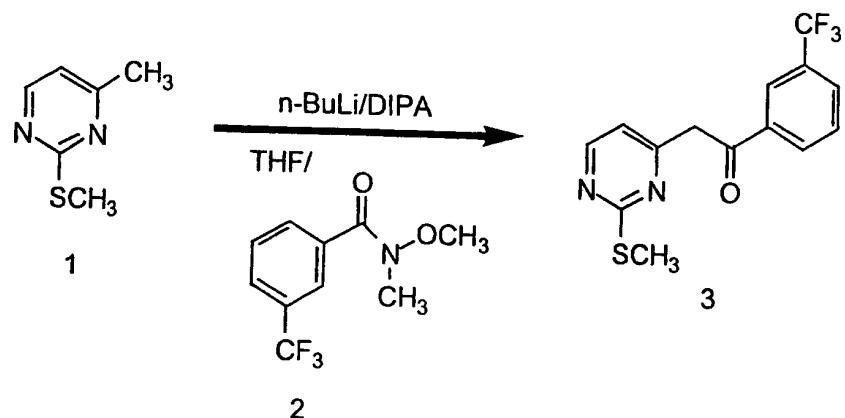
5 a sterile aqueous solution optionally containing a bactericide and
may
be prepared by methods similar to those for the preparation of
drops. Lotions or liniments for application to the skin may also
include an agent to hasten drying and to cool the skin, such as an
alcohol or acetone, and/or a moisturizer such as glycerol or an oil
10 such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in
15 solution or suspension in an aqueous or non-aqueous liquid, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its
20 derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol or macrogels. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as sorbitan esters or polyoxyethylene derivatives thereof.
25 Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicas, and other ingredients such as lanolin may also be included.

EXAMPLE 1

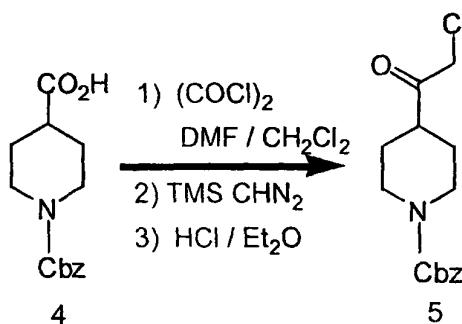
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α -(2-methylthiopyrimidine-4-yl)-3-trifluoromethylacetophenone (3):



Under Ar, a solution of diisopropylamine (70 mL, 0.5 mol) in THF (500 mL) was cooled to -70° C and a solution of 2.5 N n-BuLi in hexane (0.5 mol) was added dropwise. After addition, the solution was stirred for 0.5 hr at -70°C and then a solution of 1 (44 g, 0.31 mol) in THF (25 mL) was added dropwise. After 0.75 hr, a solution of 2 (87.4 g, 0.38 mol) in THF (25 mL) was added dropwise. The reaction was stirred at -70°C for an additional 2 hr and then treated with a saturated solution of aqueous NaHCO₃. The aqueous layer was extracted with EtOAc (3x) and the combined organic extract was washed with brine, dried, filtered and concentrated to dryness to yield a solid. The solid was crystallized from methylene chloride-hexanes to yield 66g of impure product which was further triturated with 30% ether-hexanes to yield 45g of 3. Further chromatography of the mother liquors on a Still column (100 mm) and elution with 15% ethyl acetate-hexanes yielded another 32.6g to yield a total of 77.6g of 3.

20

EXAMPLE 24-(2-chloroacetyl)-N-carbobenzoxyptiperidine: (5):

25

Under Ar, the acid 4 was dissolved in methylene chloride (500 mL) with DMF (0.5 mL) and the solution cooled to 0-

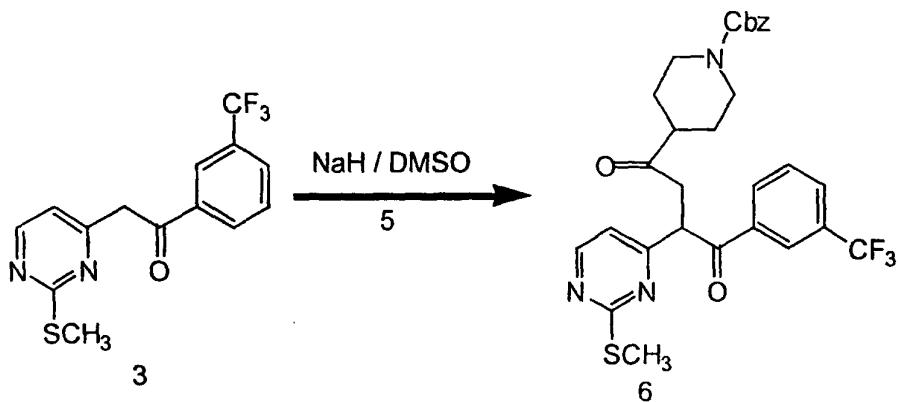
4°C. Then oxalyl chloride (5.5 mL, 63 mmol) was added dropwise. After addition, the reaction was stirred at ambient temperature for 3h, concentrated to dryness and the residue was treated with THF (100 mL) and acetonitrile (100 mL). The solution was cooled 5 to 0-4°C and a solution of 2.0M trimethylsilyldiazomethane in Et₂O (25 mL, 50 mmol) was added dropwise. After addition, the reaction was stirred at 0-4°C for 1h and then at ambient temperature for 1h. Then the solvent was removed under reduced pressure (20mm) and the residue was dissolved in Et₂O (200 mL), 10 cooled to 0-4°C and treated dropwise with 1.0M HCl in Et₂O (50 mL, 50 mmol.) with N₂ evolution. After addition, the ice bath was removed and the reaction stirred at ambient temperature. After 15h, a solution of saturated NaHCO₃ was added. The layers were separated and the aqueous layer was further extracted with 15 EtOAc (2x). The combined organic extracts were dried, filtered and concentrated to dryness. The residue was chromatographed on a Still column (80mm) and the product eluted with 20 EtOAc hexanes to yield 7.6g of 5.

20

EXAMPLE 3

25

4-(3-trifluoromethylphenyl) -4-oxo -3-(2-methylthiopyrimidin-4-yl) -1-oxo-1-N-carbobenzoxy piperidin-4-yl) butane (6):



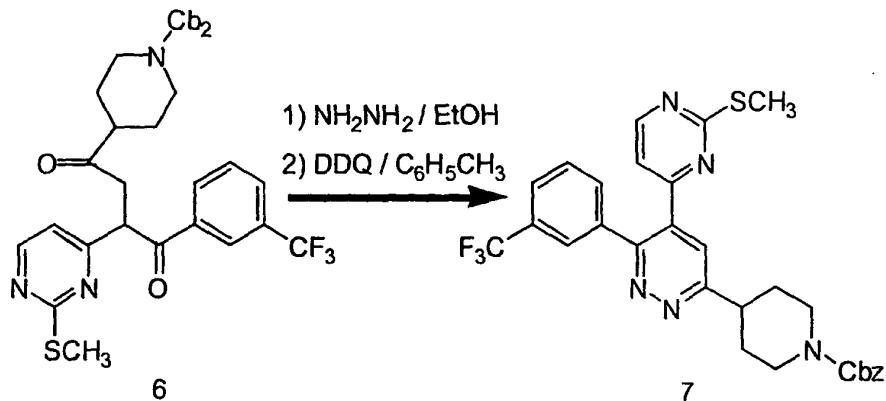
Under Ar, a solution of 3 (5.0 g, 16.0 mmol) in DMSO (30 mL) was added dropwise to a suspension of 95% NaH (0.42g, 5 17.6mmol) in DMSO (20 mL) cooled in an ice bath. After 20 min., a solution of 5 (5.2 g, 17.6 mmol) in DMSO (20 mL) was added in a steady stream. After addition, the solution was stirred at ambient temperature. After 15h, the reaction was poured into saturated NaHCO₃. The 10 aqueous was extracted with Et₂O (3x). The organic extracts were washed with H₂O (2x), brine, dried, filtered, and concentrated to dryness. The residue was chromatographed on a Still column and the product eluted with 40% EtOAc - hexanes to yield 5.2 g of 6.

15

EXAMPLE 4

3 -(3-trifluoromethylphenyl) -4 -(2-methylthiopyrimidin-4-yl)-6-(N-carbobenzoxy)piperidin-4-yl)pyridazine (7):

20

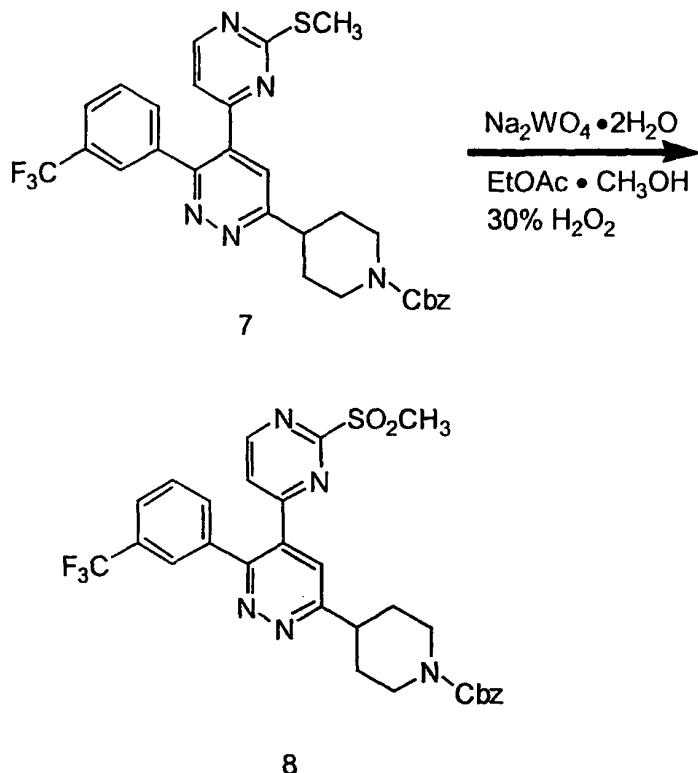


Under Ar, a solution of **6** (5.3 g, 9.3 mmol) in EtOH (150 mL) was stirred at ambient temperatures and then hydrazine (0.6 mL, 19 mmol) was added. After 3h, the EtOH was concentrated off under reduced pressure (20 mm). The residue was treated with H₂O and the aqueous solution extracted with EtOAc(3x). The combined extracts were washed with brine, dried, filtered and concentrated to dryness. The residue (6.0 g) was dissolved in toluene (180 mL) and treated with DDQ (2.3 g, 10.1 mmol) and dark colored suspension stirred at ambient temperature. After 72h, the reaction mixture was concentrated to dryness with silica gel (50 g) and the residue placed on a Still column (70 mm) and the product eluted with 70% EtOAc - hexanes to yield 4.6 g of **7**.

15

EXAMPLE 5

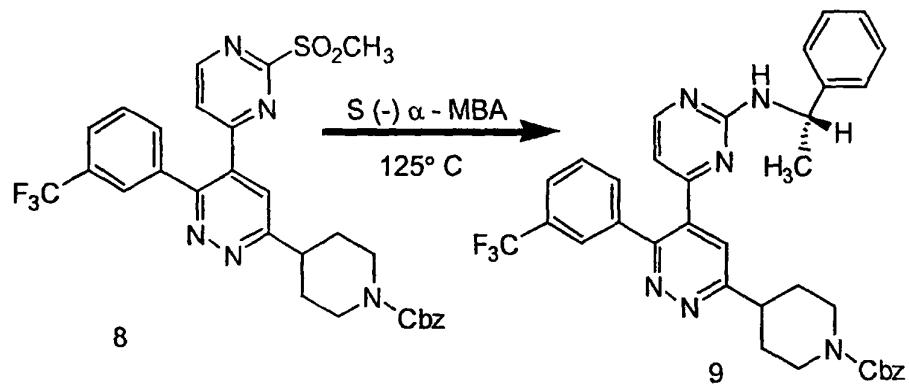
3-(3-trifluoromethylphenyl)-4-(2-methylsulfonyl)pyrimidin-4-yl-6-(N-carbobenzoxy)piperidin-4-yl)pyridazine (8):



Under Ar, a mixture of 7 (4.6 g, 8.1mmol), CH₃OH (30 mL), EtOAc (90 mL) and Na₂WO₄ • 2H₂O (360 mg, 1.1 mmol) was stirred at ambient temperature while 30% H₂O₂ (3.7 mL., 32.6 mmol) was added. After the addition, the mixture was heated at reflux for 15h, poured in saturated NaHCO₃ solution and the aqueous extracted with EtOAc (3x). The combined organic extracts were backwashed with brine, dried, filtered and concentrated to dryness to yield 4.5 g of 8.

EXAMPLE 6

15 (S) 3-(trifluoromethylphenyl)-4-[(2-α-methylbenzylamino)pyrimidin-4-yl]-6-(N-carbobenzoxy)piperidin-4-yl)pyridazine (9):



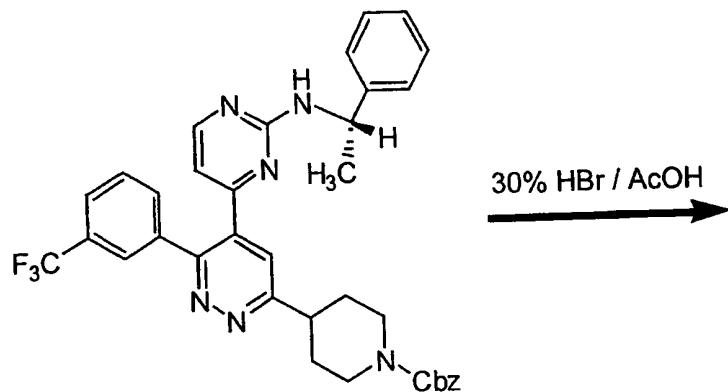
Under Ar, a mixture of 8 (4.5 g, 7.6 mmol) and S (-) α -methylbenzylamine (11.4 mL, 88 mmol) was heated at 125°C for 3h.

5 After standing overnight at ambient temperature the mixture was chromatographed on a Still column (100 mm) and the product eluted with 60% EtOAc-hexanes to yield 4.0g of 9.

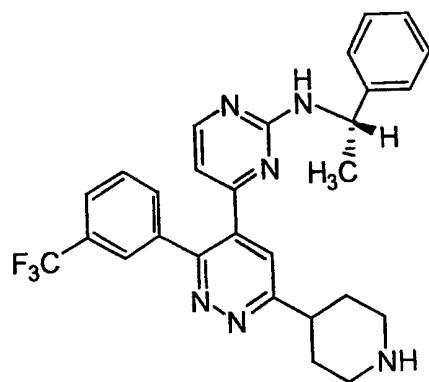
10

EXAMPLE 7

(S) 3-trifluoromethylphenyl-4-[(2-(α -methylbenzylamino)pyrimidin-4-yl]-6-(piperidin-4-yl)pyridazine (10):



9



10

Under Ar, a solution of 9 (3.1 g, 4.9 mmol), 30% HBr-AcOH (30 mL) and methylene chloride (10 mL) was stirred at ambient temperature. After 3h, 3N HCl was added and the solution extracted with Et₂O (2x). The aqueous layer was basified with solid Na₂CO₃ and extracted with EtOAc (3x). The combined extracts were dried, filtered and concentrated to dryness. The residue was dissolved in EtOAc and treated with 1N HCl in Et₂O (10 mL) and the solution was concentrated to dryness, triturated with Et₂O and filtered to yield 0.46 g of 10.

Analysis calculated for $C_{28}H_{27}N_6F_3 \cdot 2HCl \cdot H_2O$.

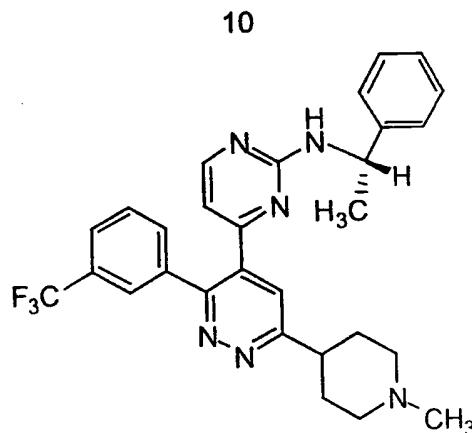
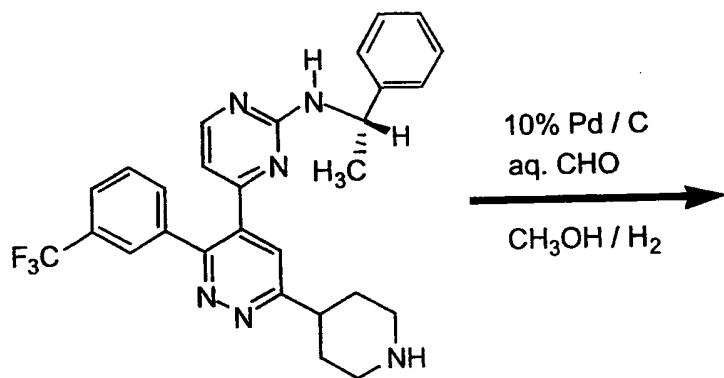
C, 56.47; H, 5.25; N, 14.11

Found: C, 56.72; H, 5.54; N, 13.61

5 MS (M+1) = 505.5

EXAMPLE 8

10 (S) 3-trifluoromethylphenyl-4-[2-(α -methylbenzylamino)pyrimidin-4-yl]-6-(N-methyl)piperidin-4-yl)pyridazine (11):



Under an atmosphere of H₂, a suspension of 10 (2.0 g, 4 mmol), methanol (30 mL), 36-38% aqueous formaldehyde (2.2 mL) and 10% Pd on carbon (370 mg) was stirred at ambient temperature. After 20h, the suspension was filtered under an atmosphere of N₂ through celite, and the filtrate was concentrated to dryness. The residue was chromatographed on a Still column (80 mm) and the product eluted with 2.5% methanol-chloroform saturated with NH₃. The common fractions were concentrated to dryness and the residue treated with 3N HCl.

5 The aqueous solution was extracted with Et₂O (2x), basified, and extracted with EtOAc (3x). The EtOAc layers were dried, filtered and concentrated to dryness. The residue was dissolved in methylene chloride-cyclohexane and treated with 1N HCl in Et₂O. The solution was concentrated to dryness and the residue

10 15 triturated with Et₂O, filtered and dried in vacuo to yield 0.9 g of 11.

Analysis calculated for C₂₉H₂₉F₃N₆ •HCl• 1.5H₂O.

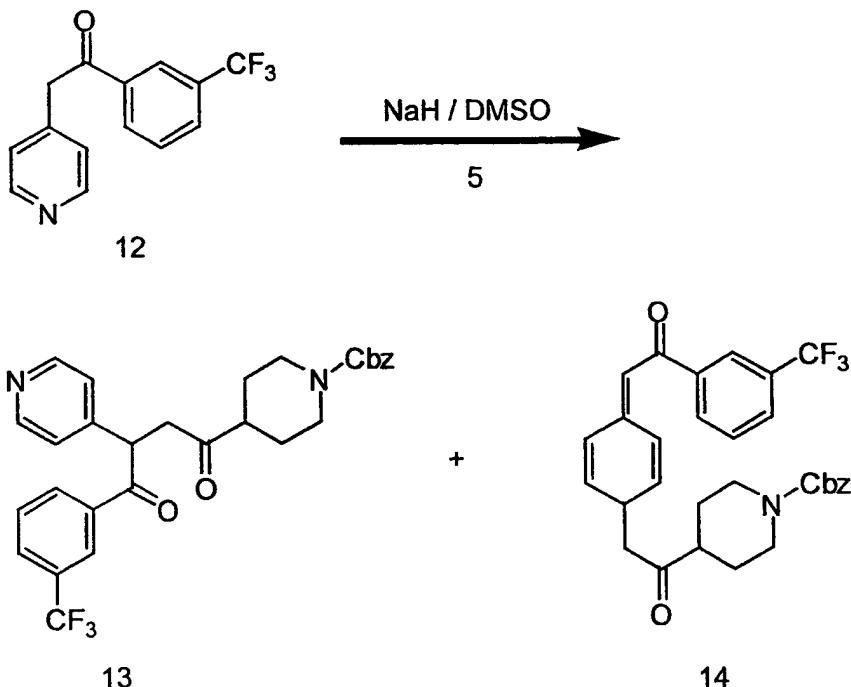
C, 59.84; H, 5.71; N, 14.44.

20 Found: C, 59.88; H, 5.33; N, 14.19.

MS (M+1) = 519.3

EXAMPLE 9**4-(3-trifluoromethylphenyl)-4-oxo-3-(pyridin-4-yl)-1-oxo-1-(N-carbobenzoxypiperidin-4-yl)butane (13):**

5



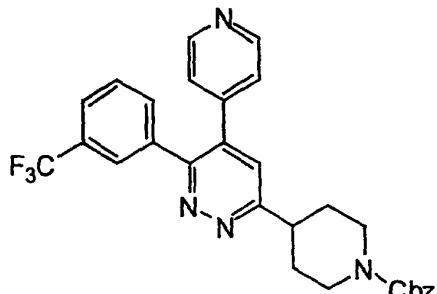
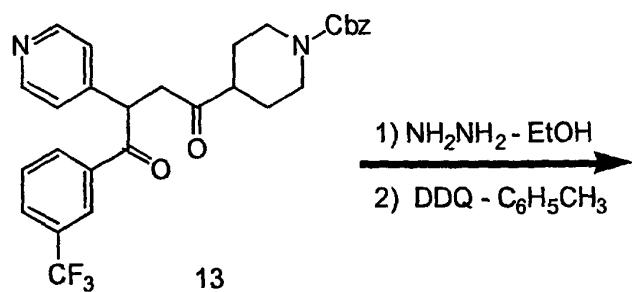
Under Ar, a solution of 12 (8.1g, 30.6 mmol) in DMSO (100 mL) was treated with 95% NaH (0.9 g, 35.5 mmol) and stirred at ambient temperature. After 1h, a solution of 5 (9.1 g, 30.7 mmol) in DMSO (100 mL) was added dropwise. After 18h, 2N AcOH (100 mL) was added and the solution then poured carefully into a saturated Na₂CO₃ solution. The aqueous solution was extracted with EtOAc (4x). The combined organics were backwashed with saturated Na₂CO₃, water, brine, and dried, filtered and concentrated to dryness. The residue was triturated with Et₂O, and then filtered to yield 8.6 g (54%) of 14 as a yellow-orange solid. The mother liquor was chromatographed on a Still column (100

mm) and the product eluted with 65-90% EtOAc - hexanes to yield 2.2 g of 13.

5

EXAMPLE 10

3-(3-trifluoromethylphenyl)-4-(pyridin-4-yl)-6-(N-carbobenzoxyphiperidin-4-yl)pyridazine (15):



10

Under Ar, a solution of 13 (2.2 g, 4.2 mmol) in EtOH (50 mL) was treated with hydrazine (306 mg, 9.6 mmol). After 4h, the reaction was concentrated to dryness and the residue was 15 partitioned between water-EtOAc (3x). The EtOAc extracts were backwashed with brine, dried, filtered and concentrated to dryness. The residue was dissolved in toluene (60mL) and 2,3 dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1.0 g, 4.5 mmol) was

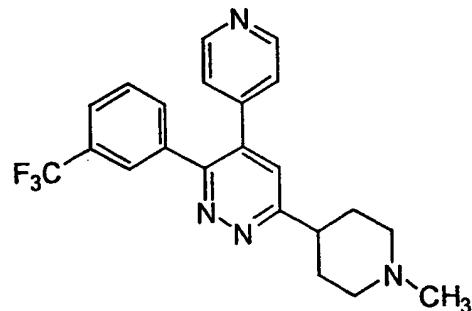
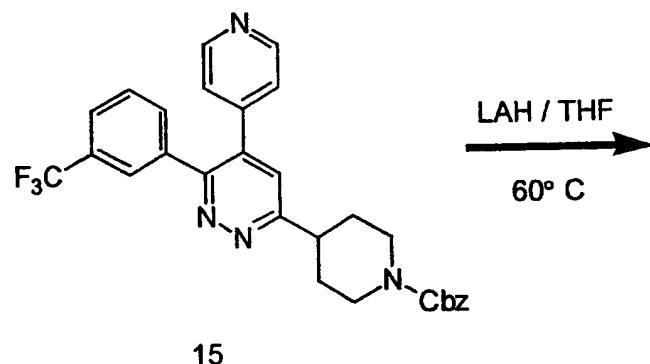
added. After 0.5h, the reaction was chromatographed on a Still column (60 mm) and the product eluted with 90-100% EtOAc-hexanes to yield 1.6 g of 15.

5

EXAMPLE 11

10

3-(3-trifluoromethylphenyl)-4-(pyridine-4-yl)-6-(N-methylpiperidin-4-yl)pyridazine (16):



Under Ar, a solution of 15 (0.73 g, 1.4 mmol) in THF (175 mL) was treated with LAH (0.37 g, 9.7 mmol). After addition, the reaction was heated at 60° C. After 2h, the reaction was

cooled to room temperature and treated with saturated Na_2SO_4 until a suspension results. The reaction mixture was filtered and the filtrate washed with EtOAc . The organic was washed with H_2O , brine, dried, filtered and concentrated to dryness. The residue was treated with Et_2O -hexanes, filtered and dried to yield 0.3 g of 16; mp 188-9°C.

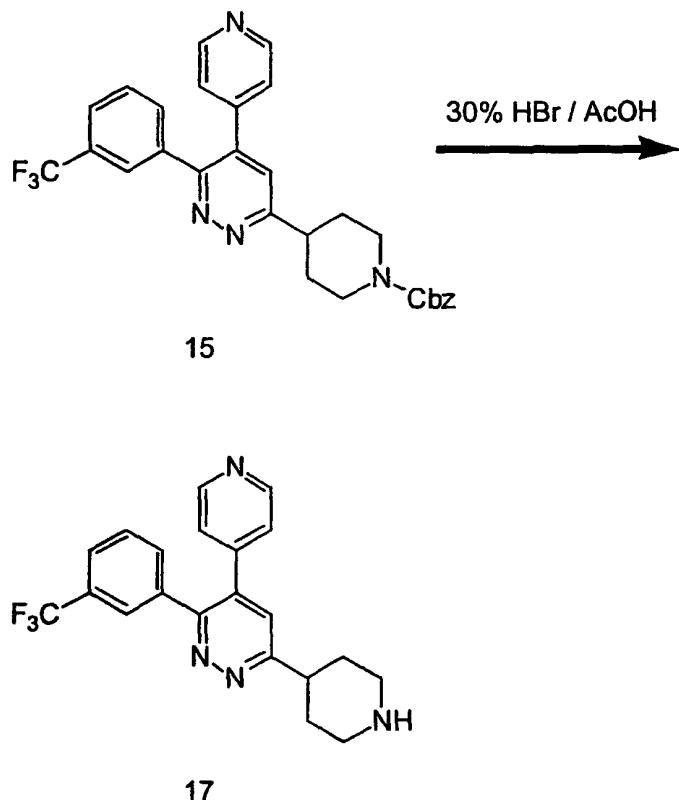
-5

Analysis calculated for $\text{C}_{22}\text{H}_{21}\text{N}_4\text{F}_3$
C, 64.99; H, 5.43; N, 13.78.

10 Found: C, 65.29; H, 5.83; N, 14.06.

EXAMPLE 12

15 3-(trifluoromethylphenyl)-4-(pyridin-4-yl)-6-(piperidin-4-yl) pyridazine (17):



Under Ar, a mixture of 15 (0.87 g, 17 mmol) in 30% HBr

5 in AcOH (10mL) was stirred at ambient temperatures. After 1.5h, the reaction was poured into 3N HCl and extracted with Et₂O (2x). The aqueous layer was basified carefully with a saturated Na₂CO₃ solution until basic and then extracted with EtOAc (3x). The combined EtOAc layers were dried, filtered and concentrated to dryness. The residue was chromatographed on a Still column (50 mm) and the product eluted with chloroform saturated with NH₃ to yield 0.4 g of 17. The product was treated with 1N HCl in EtOH, concentrated to dryness and triturated with Et₂O, filtered and dried to yield the hydrochloride salt; mp 218-20°C.

10

15

Analysis calculated for C₂₁H₁₉F₃N₄ • 3 HCl • 1/2 H₂O.

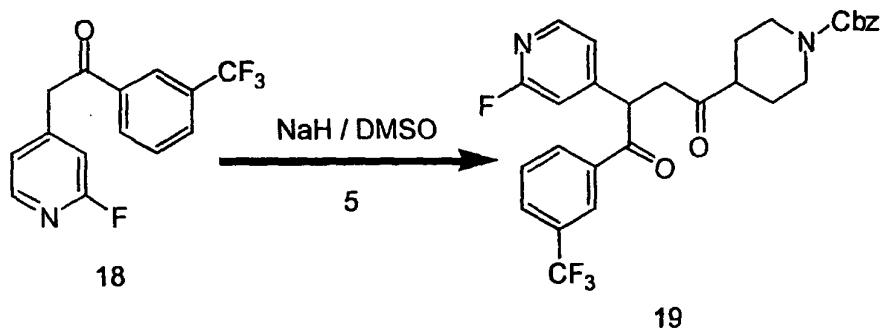
C, 50.16; H, 4.61; N, 11.14.

Found: C, 49.96; H, 4.76; N, 11.15.

EXAMPLE 13

5

4-(3-trifluoromethylphenyl)-4-oxo-3-(2-fluoropyridin-4-yl)-1-oxo-1-(N-carbobenzoxyphiperidin-4-yl)butane (19):



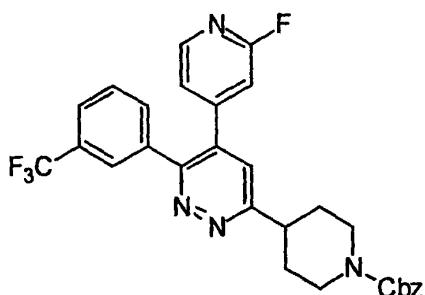
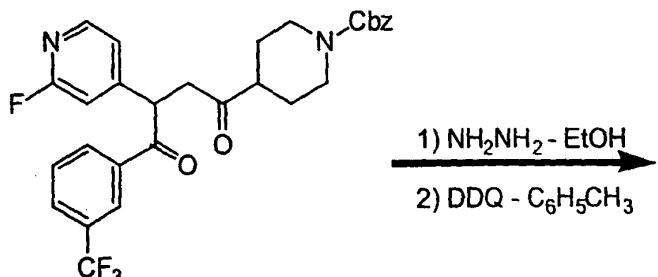
10

Under Ar, a solution of 18 (4.0 g, 14.1 mmol) in DMSO (30 mL) was treated with 95% NaH (0.4 g, 15.8 mmol) while the reaction was stirred at room temperature. After a 1/2 h, a solution of 5 (5.0 g, 16.9 mmol.) in DMSO (40 mL) was added dropwise and the solution stirred at room temperature. After 18h, the reaction was poured into 2N HCl (50 mL) and then basified with saturated Na₂CO₃ and then extracted with EtOAc (3x). The organic extracts were backwashed with H₂O, brine, dried, filtered and concentrated to dryness to yield 8.8 g of 19.

EXAMPLE 14

25

3-(3-trifluoromethylphenyl) 4-(2-fluoropyridin-4-yl)-6-(N-carbobenzoxyphiperidin-4-yl)pyridazine (20):

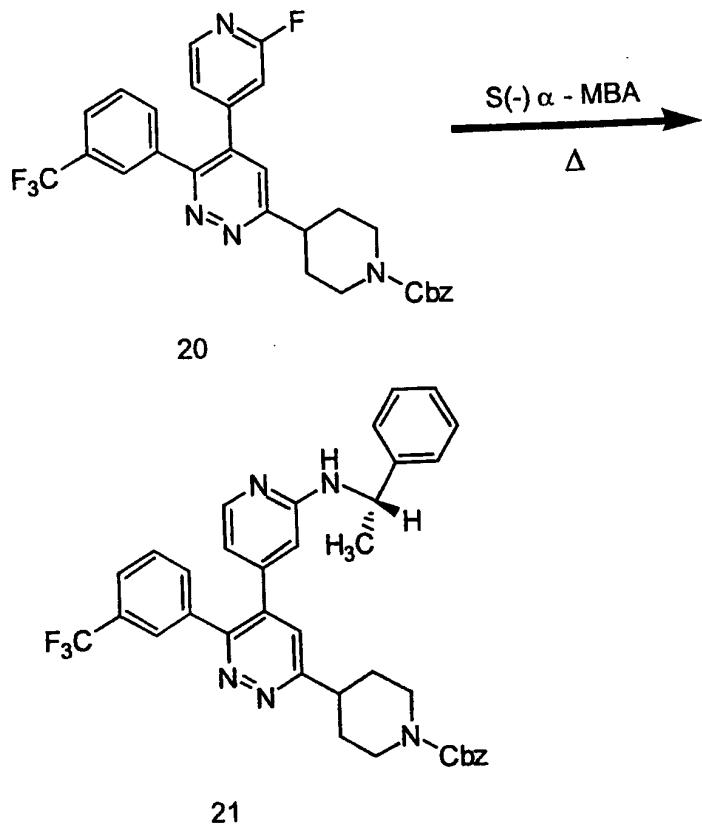


Under Ar, a solution of 19 (8.8 g, 14.1 mmol) in EtOH (270 mL) was stirred at room temperature and treated with 5 hydrazine (1.4 g, 42.1 mmol). After 2h, the reaction was concentrated to dryness. The reaction was partitioned between H₂O and EtOAc (3x). The organic extracts were backwashed with brine, dried, filtered and concentrated to dryness. The residue was dissolved in toluene (400 mL) and 10 treated with DDQ (3.4 g, 14.9 mmol). After stirring at room temperature for 3h, the reaction was concentrated to dryness. The residue was chromatographed on a Still column (100 mm) and the product eluted with 60% EtOAc-hexanes to yield 5.5 g of 20.

15

EXAMPLE 15

(S) 3-(3-trifluoromethylphenyl) 4-[(2-(α - methylbenzylamino) pyridin-4-yl]-6-(N-carbobenzoxy piperidin-4-yl) pyridazine (21):



5

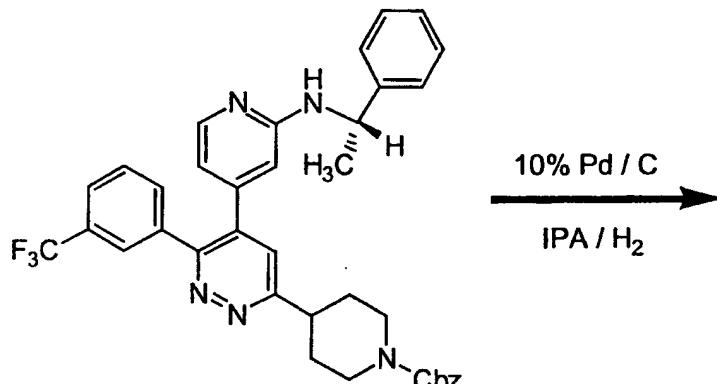
Under Ar, a mixture of 20 (1.6 g, 3.0 mmol) and S (-) α - methylbenzylamine (8 mL) was heated at 180° C for 1.0 h. The reaction was then chromatographed on a Still column (100 mm) and the product elected with 50-60% EtOAc-hexanes to yield 1.0 g of 21.

10

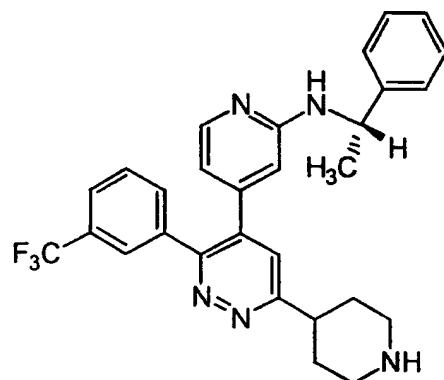
EXAMPLE 16

15

(S)-3-(3-trifluoromethylphenyl)-4-[(3-(α -methylbenzylamino)pyridin-4-yl]-6-(piperidin-4-yl)pyridazine (22):



21



22

5

A solution of 21 (0.7 g, 1.1 mmol) in isopropanol (50 mL) was placed in a Parr apparatus under Ar, and 10% Pd on C (200 mg) was added. The suspension was hydrogenated at 6 psi of H₂. After shaking overnight on the Parr apparatus, the 10 suspension was filtered under Ar through super-cel and the pad washed with EtOAc. The filtrate was concentrated to dryness.

The residue was chromatographed on a Still column (50 mm) and the product eluted with 3% CH₃OH-chloroform saturated with NH₃ to yield 0.24 g of 22.

5 Analysis calculated for C₂₉H₂₈F₃N₅ • 0.25 H₂O.

C, 68.55; H, 5.65; N, 13.79.

Found: C, 68.36; H, 5.67; N, 13.75.

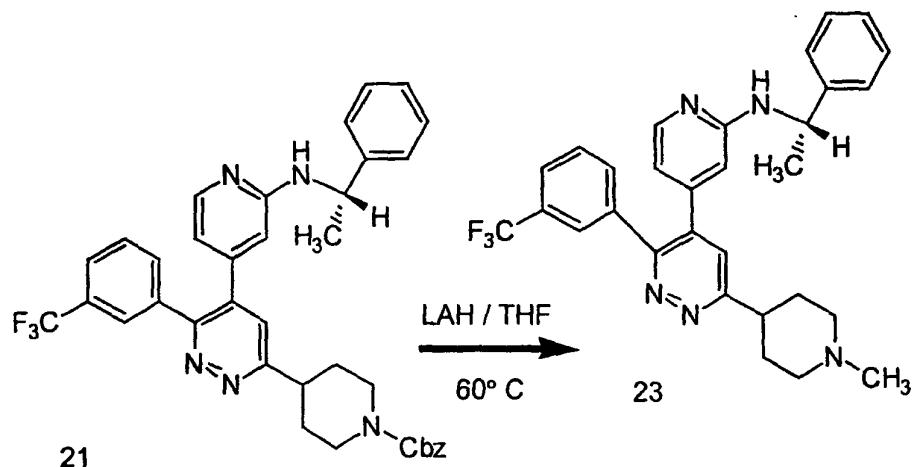
MS (M+1) = 504.2612

10

EXAMPLE 17

(S) 3-(3-trifluoromethylphenyl)-4-[2-(α -methylbenzylamino)pyridin-4-yl]-6-(N-methylpiperidin-4-yl)pyridazine (23):

15



Under Ar, a solution of 21 (0.8 g, 1.2 mmol) in THF (50 mL) was treated with LAH (0.3 g, 7.9 mmol) and heated to 50°C.

20 After 2hrs, the reaction was cooled to room temperature and treated with saturated Na₂SO₄ until a white suspension resulted. The suspension was filtered through super-cel and the pad washed with EtOAc. The organic extracts were concentrated to

dryness and the residue chromatographed on a Still column (50 mm) and the product eluted with chloroform saturated with NH₃. The residue was dissolved in EtOAc and treated with 1N HCl in Et₂O concentrated to dryness and the residue was stirred with 1:1 5 EtOAc-Et₂O (20 mL), cooled in an ice bath and filtered. The solid was dried *in vacuo* to yield 350 mg of 23.

Analysis calculated for C₃₀H₃₀F₃N₅•2HCl• 1.5 H₂O.

C, 58.34; H, 5.71; N, 11.34.

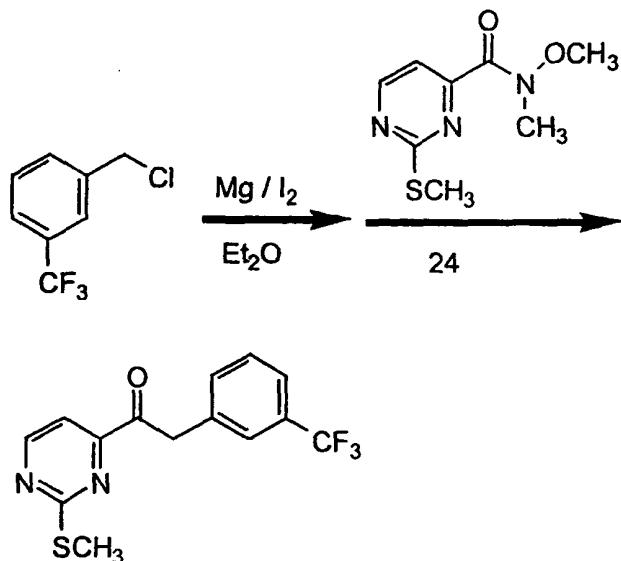
10 Found: C, 58.56; H, 5.82; N, 10.72.

MS(M+1) = 518.31

EXAMPLE 18

15

1-(2-methylthiopyrimidin-4-yl)-1-oxo-2-(3-trifluoromethylphenyl)ethane (25):



20

Under Ar, a solution of 3-trifluoromethylbenzyl chloride (12 mL, 77 mmol) in Et₂O (75 mL) was added dropwise to a mixture of Mg turnings (1.7 g, 71 mmol), Et₂O (75mL) and cat. I₂.

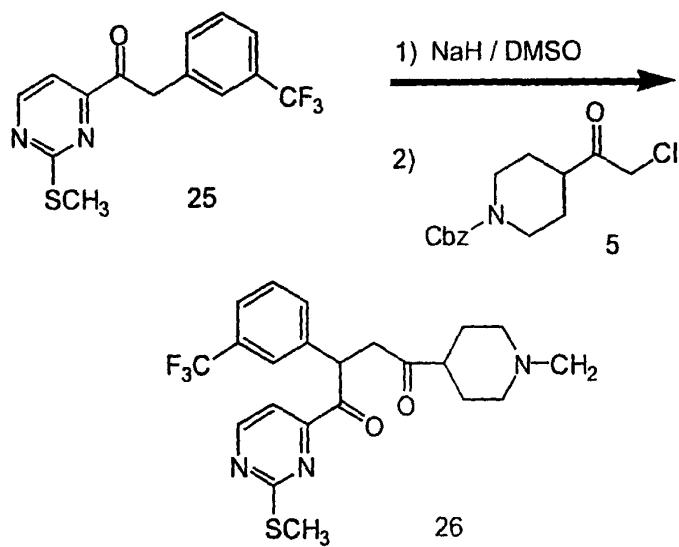
The mixture was heated at reflux for 0.5h, stirred at room temperature over 1h and then a solution of 24 (9.3 g, 44 mmol) in Et₂O (75 mL) was added dropwise. After refluxing for 4h, the reaction was cooled to room temperature and treated with 2N 5 HCl. The aqueous was extracted with Et₂O (1x) and EtOAc (2x). The combined extracts were backwashed with H₂O, brine, dried, filtered and concentrated to dryness. The residue was chromatographed on a Still column (100 mm) and the product eluted with 20% EtOAc-hexanes to yield 3.5 g of 25.

10

EXAMPLE 19

1-(2-methylthiopyrimidin-4-yl)-1-oxo-2-(3-trifluoromethylphenyl)-4-oxo-4-(N-carbobenzyloxypiperidin-4-yl)butane (26):

15



Under Ar, a solution of 25 (4.0 g, 12.8 mmol) in DMSO (30 mL) was treated with 95% NaH (0.35 g, 13.8 mmol). After 20 stirring at room temperature for 15 min, a solution of 5 (3.9 g, 13.2 mmol) in DMSO (20 mL) was added in one portion to the deep red

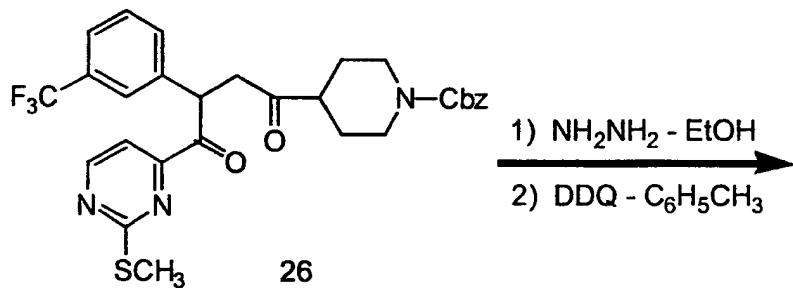
solution. After stirring at room temperature for 18h, 2N AcOH was added and then poured carefully in saturated Na_2CO_3 . The basic aqueous solution was extracted with EtOAc (3x). The organic extracts were backwashed with H_2O , brine, dried, filtered and concentrated to dryness. The residue was chromatographed on a Still column (80 mm) and the product was eluted with 30% EtOAc -hexanes to yield 1.5 g of 26.

5

10

EXAMPLE 20

3-(2-methylthiopyrimidin-4-yl)-4-(3-trifluoromethylphenyl)-6-(N-carbobenzoxypiperidin-4-yl)pyridazine (27):



15

Under Ar, a solution of 26 (1.5 g, 2.6 mmol) in EtOH (50 mL) was treated with hydrazine (0.5 mL, 16 mmol). After 5h, the reaction was concentrated to dryness. The residue was treated with H_2O and extracted with EtOAc (3x). The EtOAc extracts were dried, filtered and concentrated to dryness. The residue was

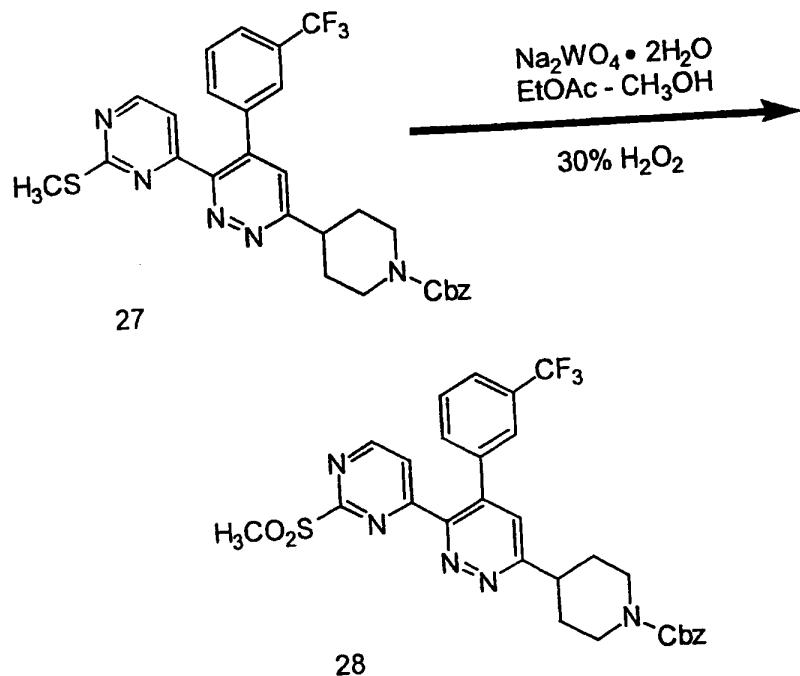
20

dissolved in toluene (100 mL) and treated with DDQ (0.62 g, 2.7 mmol). After 0.5h, the dark colored reaction was concentrated to dryness. The residue was chromatographed on a Still column (50 mm) and the product eluted with 40% EtOAc-hexanes to yield 1.2 g of 27.

5 of 27.

EXAMPLE 21

10 3-(2-methylsulfonylpyrimidin-4-yl)-4-(3-trifluoromethylphenyl)-6-(N-carbobenzoxyperidin-4-yl)pyridazine (28):

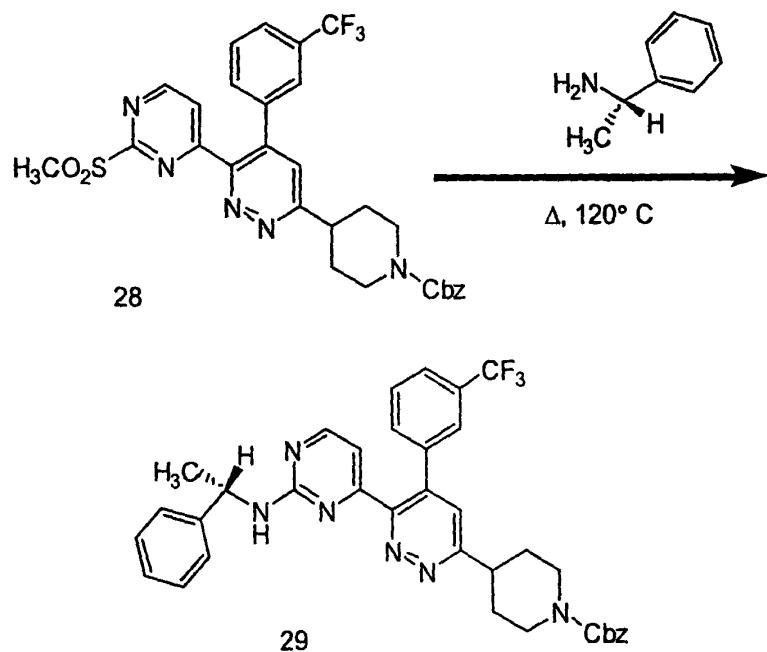


15 Under Ar, a solution of 27 (1.2g, 2.1 mmol) in CH_3OH (10 mL) and EtOAc (30 ml) was added $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ (100 mg, 0.3 mmol) and 30% H_2O_2 (1.3 mL, 11 mmol) and the mixture heated at reflux. After 18h, a saturated solution of NaHSO_3 was added to

destroy excess peroxides and the aqueous extracted with EtOAc (3x). The organic extracts were dried, filtered and concentrated to dryness. The residue was chromatographed on a Still column (60 mm) and the product eluted with 90% EtOAc-hexanes to yield 5 0.61 g of 28.

EXAMPLE 22

10 (S) 3-[2-(α -methylbenzylamino)pyrimidin-4-yl]-4-(3-trifluoromethylphenyl)-6-(N-carbobenzoxypiperidin-4-yl)pyridazine (29):



15

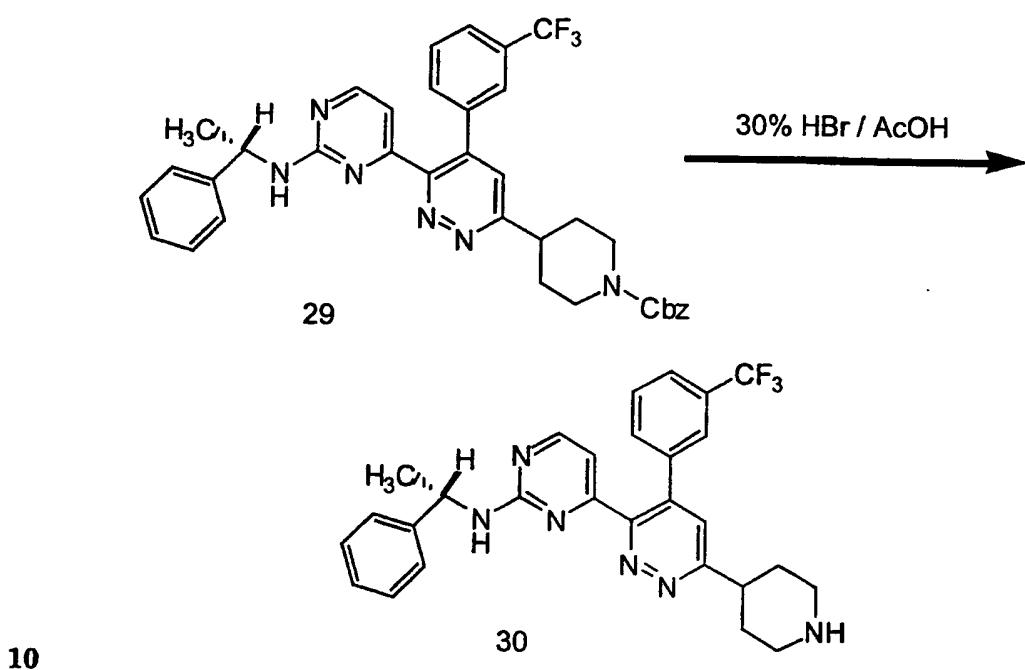
Under Ar, a mixture of 28 (0.62 g, 1.0 mmol) and (S) (-)- α -methylbenzylamine (1.5 mL, 11.6 mmol) was heated at 120° C for 3h. The reaction was chromatographed on a Still column (40 mm)

and the product eluted with 80% EtOAc-hexanes to yield 0.6 g of 29.

5

EXAMPLE 23

(S) 3-[2-(α -methylbenzylamino)pyrimidin-4-yl]-4-(3-trifluoromethylphenyl)-6-(piperidin-4-yl)pyridazine (30):



Under Ar, a solution of 29 (0.3 g, 0.47 mmol) in 30% HBr-AcOH (5 mL) was stirred at room temperature for 1h. The reaction was then treated with 2N HCl and extracted with Et₂O (2x). The resulting aqueous was then basified with saturated Na₂CO₃ and extracted with EtOAc (3x). The organic extracts were dried, filtered and concentrated to dryness. The residue was chromatographed on a Still column (40 mm) and the product eluted with 5% CH₃OH CHCl₃ saturated with NH₃ to yield 70 mg of 30.

Analysis calculated for $C_{28}H_{27}F_3N_6$ - H_2O .

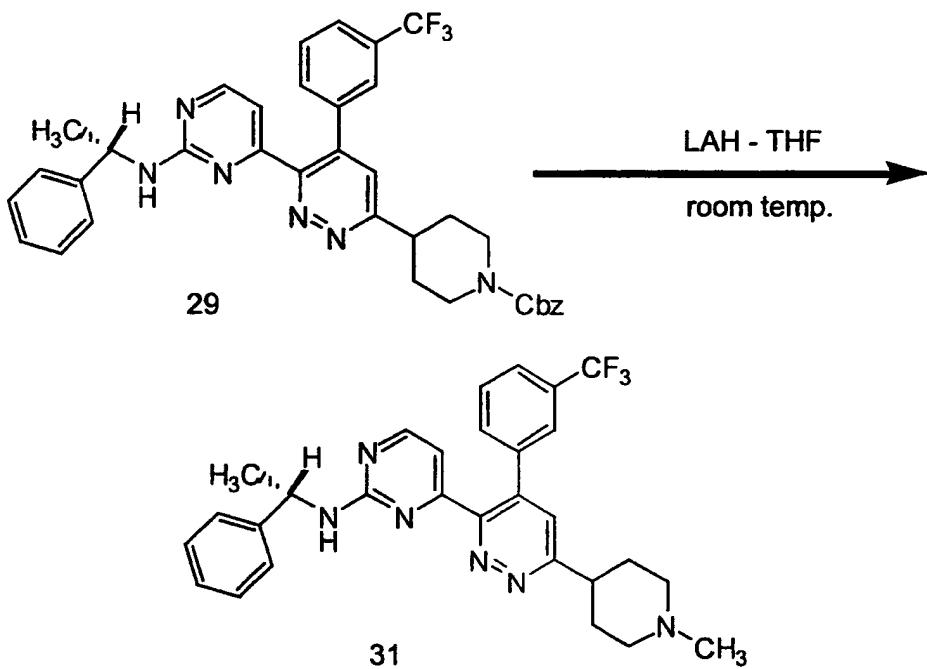
C, 63.26; H, 5.88; N, 15.81

Found: C, 63.82; H, 5.40; N, 15.33

5 Mass spectra (M+1) = 505.21

EXAMPLE 24

10 (S) 3-[2-(α -methylbenzylamino)pyrimidin-4-yl]-4-(3-trifluoromethylphenyl)-6-(N-methylpiperidin-4-yl)pyridazine (31):



15 Under Ar, a solution of 29 (0.28 g, 0.44 mmol) in THF (50 mL) was treated with LAH (140 mg, 3.7 mmol) at room temperature. The reaction was then treated carefully with saturated Na_2SO_4 until a white suspension resulted. The mixture was filtered through super-cel and the pad was washed with EtOAc. The filtrate was concentrated to dryness. The residue

was chromatographed on a Still column (40 mm) and the product eluted with methylene chloride saturated with NH₃. The common fractions were pooled and concentrated to dryness. The residue was treated with 1N HCl in Et₂O, concentrated to dryness,
 5 triturated with Et₂O, concentrated to dryness, triturated with Et₂O, and filtered to yield 85mg of 31.

Analysis calculated for C₂₉H₂₉F₃N₆ • 2HCl • 1.25 H₂O.

C, 56.72; H, 5.50; N, 13.69.

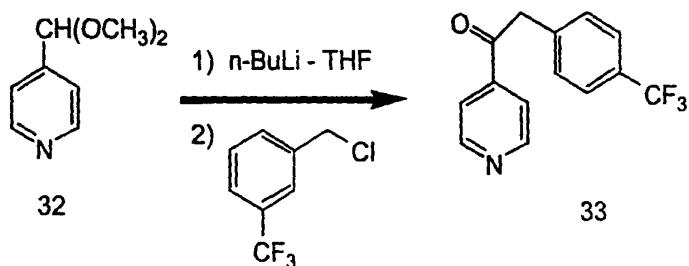
10 Found: C, 56.94; H, 5.67; N, 13.04.

MS (M+1) = 519.27

15

EXAMPLE 25

1-(pyridin-4-yl)-1-oxo-2-(3-trifluoromethylphenyl)ethane (33):



20

Under Ar, a solution of 32 (5.0 g, 32.7 mmol) in THF (50 mL) was cooled to -78°C and treated dropwise with 2.5N n-BuLi in hexane (14 mL, 35 mmol). After the addition, the solution was stirred for 15 min at

25 -78° C and then 3-trifluoromethylbenzyl chloride (5.4 mL, 6.8 g, 35 mmol) was added dropwise. After the addition, the solution was stirred at 0-4°C and the deep purple color diminished to a light amber color. After 2h, the reaction was stirred at room

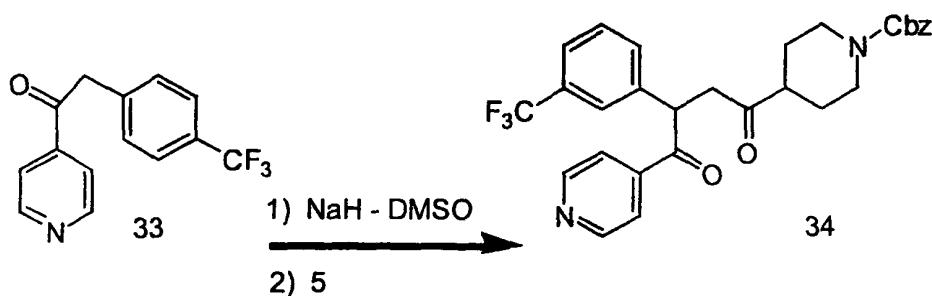
temperature for 1h and then poured into saturated NaHCO_3 , and extracted with EtOAc (3x). The organic extracts were backwashed with brine, dried, filtered and concentrated to dryness. The residue was treated with formic acid (116 mL) and 5 the mixture heated at 80°C. After 2h, the reaction was concentrated to dryness. The residue was partitioned between EtOAc (3x) - saturated NaHCO_3 . the organic extracts were backwashed with brine, dried, filtered and concentrated to dryness. The residue was chromatographed on a Still 10 column (70 mm) and the product eluted with 50% EtOAc -hexanes to yield 5.0 g (57%) of 33.

EXAMPLE 26

15

1-(pyridin-4-yl)-1-oxo-2-(3-trifluoromethylphenyl)-4-oxo-4-(N-carbobenzoxypiperidin-4-yl)butane (34):

20



25

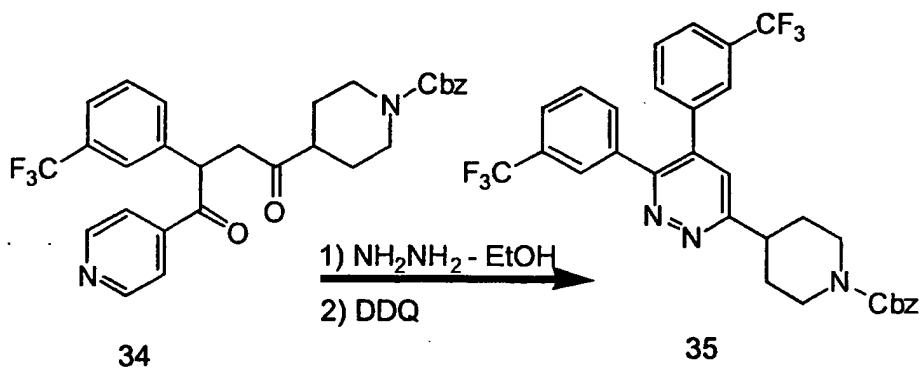
Under Ar, a solution of 33 (5.2 g, 19.6 mmol) in DMSO (65 mL) was stirred at room temperature and treated with 95% NaH (0.58 g, 22.8 mmol). After 1h, a solution of 5 (5.8 g, 19.6 mmol) in DMSO (25 mL) was added dropwise. After 18h, the reaction was poured into 2N HCl (100 mL) and then basified with saturated Na_2CO_3 and then extracted with EtOAc (3x). The combined EtOAc extracts were backwashed with H_2O , brine, dried, filtered and

concentrated to dryness. The residue was chromatographed on a Still column to yield 3.3 g of crude 34.

5

EXAMPLE 27

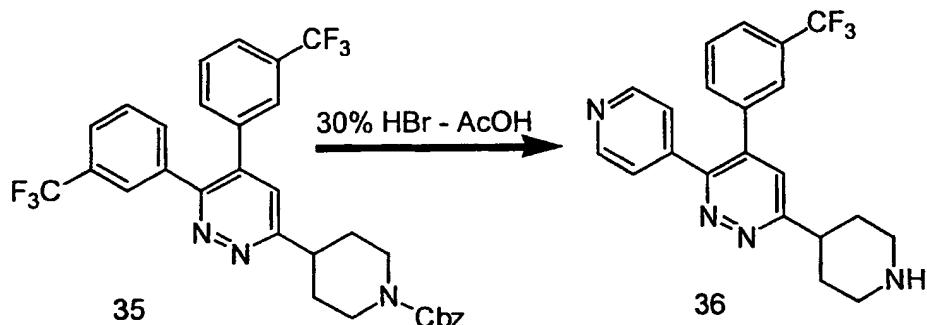
3-(pyridin-4-yl)-4-(3-trifluoromethylphenyl)-6-(N-carbobenzoxypiperidin-4-yl)pyridazine (35):



10 Under Ar, hydrazine (0.5 mL, 0.51 g, 15.9 mmol) was added to a solution of 34 (3.3 g) in EtOH (75 mL). After 4h, the solution was concentrated to dryness and the residue treated with toluene (60 mL) dioxane (60 mL) and DDQ (0.8 g, 3.5 mmol). After 15h, the reaction was concentrated to dryness. The residue
 15 was chromatographed on a Still column (50 mm) and the product eluted with 100% EtOAc to yield 1.2 g of 35.

EXAMPLE 28

20 3-(pyridine-4-yl)-4-(3-trifluoromethylphenyl)-6-(piperidin-4-yl)pyridazine (36):



Under Ar, a mixture of 35 (0.68 g, 1.3 mmol) and 30% HBr - AcOH (10 mL) was stirred at room temperature. After 3h, 3N HCl (50 mL) was added and the solution extracted with Et₂O (2x). The aqueous layer was basified with saturated Na₂CO₃ and extracted with EtOAc (6x). The organic extracts were dried, filtered and concentrated to dryness. The residue was crystallized from EtOAc-hexanes to yield 73 mg (15%) of 36; mp 148-50° C.

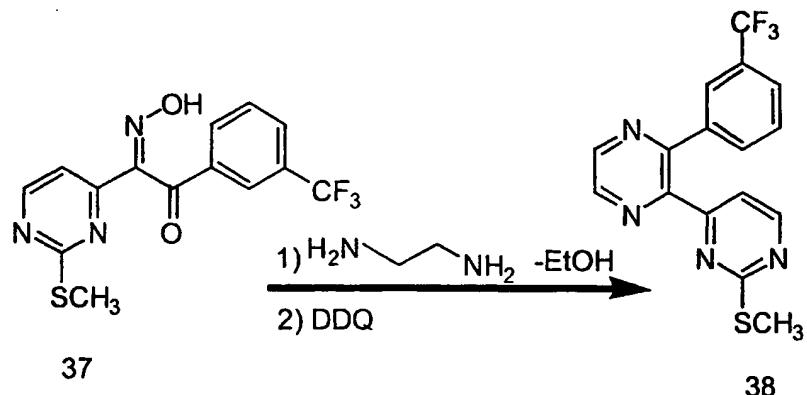
Analysis calculated for $C_{21}H_{19}F_3N_4 \cdot 2.5 H_2O$.

C, 58.73; H, 5.63; N, 13.05.

15 Found: C, 58.85; H, 5.10; N, 12.04.

EXAMPLE 29

20 2-(2-methylthiopyrimidin-4-yl)-3-(3-trifluoromethylphenyl)pyrazine (2).

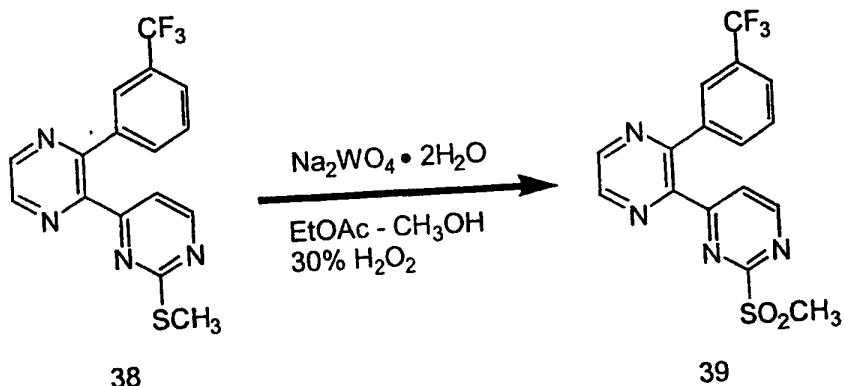


Under Ar, a solution of oxime 37 (1.0g, 2.9 mmol) in abs. EtOH (30mL) with ethylene diamine (0.27g, 4.5 mmol) and AcOH (4 drops) was heated at reflux. After 3 days, the reaction mixture was concentrated to dryness and partitioned between saturated NaHCO₃ and EtOAc (3x). The organic extracts were dried, filtered and concentrated to dryness. The residue was dissolved in toluene (80 mL) and treated with DDQ (0.66 g, 2.9 mmol). After stirring at room temperature overnight, the suspension was chromatographed on a Still column (50 mm) and the product eluted with 30% EtOAc-hexanes to yield 100 mg (10%) of 38.

EXAMPLE 30

2-(2-methylsulfonylpyrimidin-4-yl)-3-(3-trifluoromethylphenyl)pyrazine (39):

5



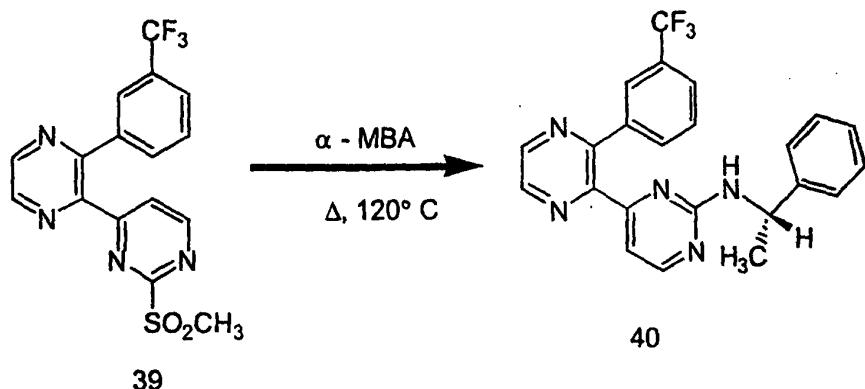
Under Ar, a solution of 38 (290 mg, 0.83 mmol) in CH₃OH (2 mL) and EtOAc (9 mL) was treated with sodium tungstate dihydrate (55 mg, 0.17 mmol) and 30% H₂O₂ (0.5 mL, 4.4 mmol). After stirring at reflux for 15h, the reaction was treated with saturated NaHSO₃ and extracted with EtOAc (3x). The organic extracts were dried, filtered and concentrated to dryness to yield 0.28 (89%) g of 39.

15

EXAMPLE 31

S-[2-(α -methylbenzylamino)pyrimidin-4-yl]3-(3-trifluoromethylphenyl)pyrazine (40):

20



Under Ar, sulfone **39** (0.28 g, 0.74 mmol) and 5-(-) α -methylbenzylamine (0.97 g, 8 mmol) were heated at 120° C. After 5 20h, the mixture was chromatographed on a Still column (50 mm) and the product eluted with 30-40% EtOAc - hexanes. The residue was treated with EtOAc and 1N HCl (3 mL), concentrated to dryness, triturated with hexanes and filtered to yield 160 mg of **40**.

10 Analysis calculated for $\text{C}_{23}\text{H}_{18}\text{F}_3\text{N}_5 \cdot \text{HCl} \cdot 0.4 \text{ Hex} \cdot 0.5 \text{ H}_2\text{O}$.

C, 60.9; H, 4.85; N, 13.61

Found: C, 60.84; H, 5.15; N, 13.97;

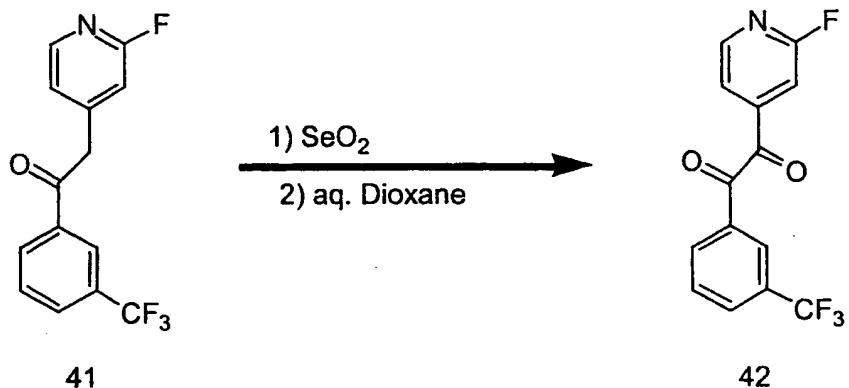
MS (M+1) = 422.1

15

EXAMPLE 32

1-(2-fluoropyridin-4-yl)1,2-dioxo-2-(3-trifluoromethylphenyl)ethane (42):

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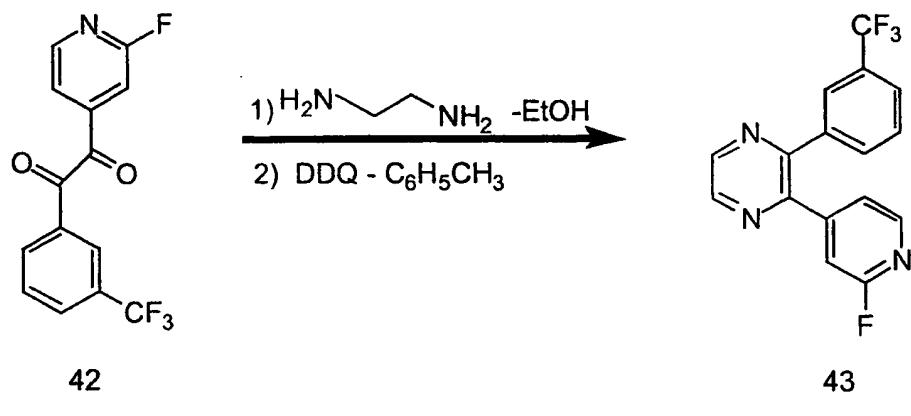


Under Ar, a solution of 41 (6.4 g, 22.6 mmol) in 5% aqueous dioxane (100 mL) was treated with SeO_2 (9.5 g, 86.5 mmol) and the mixture heated at reflux with stirring. After 2 h, the reaction was cooled to room temperature and concentrated to dryness. The residue was dry packed with silica gel (50 g) and chromatographed on a Still column (70 mm). The product was eluted with 15% EtOAc-hexanes to yield 3.35 g of 42.

10

EXAMPLE 33

2-(2-fluoropyridin-4-yl)-3-(3-trifluoromethylphenyl)pyrazine (43):

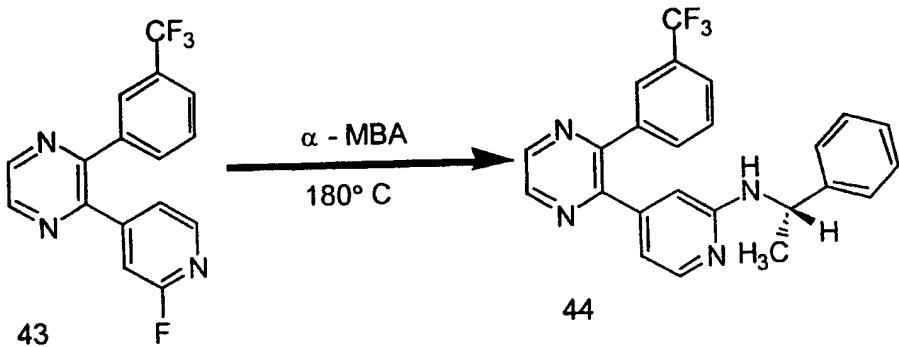


Under Ar, a solution of 42 (3.35 g, 11.3 mmol) in EtOH (150 mL) was treated with ethylene diamine (0.9 g, 15 mmol) and heated at 50°C. After 3h, the reaction was concentrated to dryness and the residue was partitioned between H₂O and EtOAc (3x). The combined organic extracts were dried, filtered and concentrated to dryness. The residue was dissolved in toluene (230 mL) and reacted with DDQ (4.0 g, 17.6 mmol). After 18h at room temperature, the reaction was heated at 60°C for 2h then treated with additional DDQ (1.0 g) and heated at 80°C for 5h. The reaction was then dry packed with silica gel (70 g) and chromatographed on a Still column (80 mm). The product was eluted with 30% EtOAc-hexanes to yield 2.85 g of 43.

EXAMPLE 34

15

(S)-2-[2-(α -methylbenzylaminopyridin-4-yl]-3-(3-trifluoromethylphenyl)pyrazine (44):



20

Under Ar, a mixture of 43 (1.1 g, 3.4 mmol) and S - (-) - α -methylbenzylamine (4.7 g, 37 mmol) was heated at 180° C. After 6 h, the mixture was chromatographed on a Still column (60 mm) and the product eluted 50% EtOAc-hexanes. The residue was treated with ethanolic-HCl, concentrated to dryness and the residue pumped dry to yield 1.2 g. of 44 as a glass.

Analysis calculated for $C_{24}H_{19}F_3N_4 \bullet HCl \bullet 1/2 H_2O$.

C, 61.87; H, 4.54; N, 12.03.

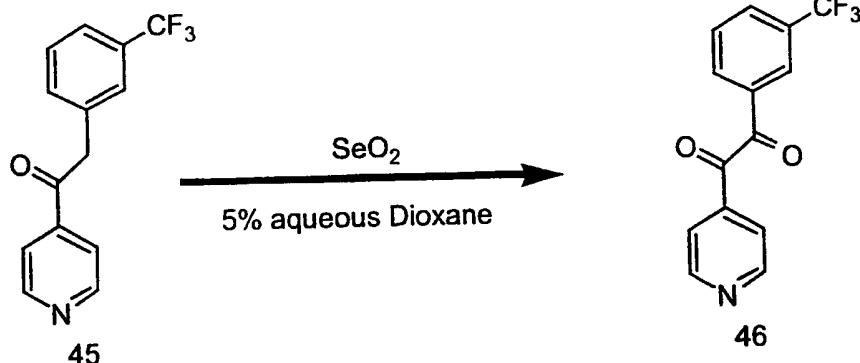
Found: C, 62.12; H, 5.02; N, 11.68.

5 MS (M+1) = 421.21

EXAMPLE 35

1-(pyridin-4-yl)-1,2-dioxo-2-(3-trifluoromethylphenyl) ethane (46):

10

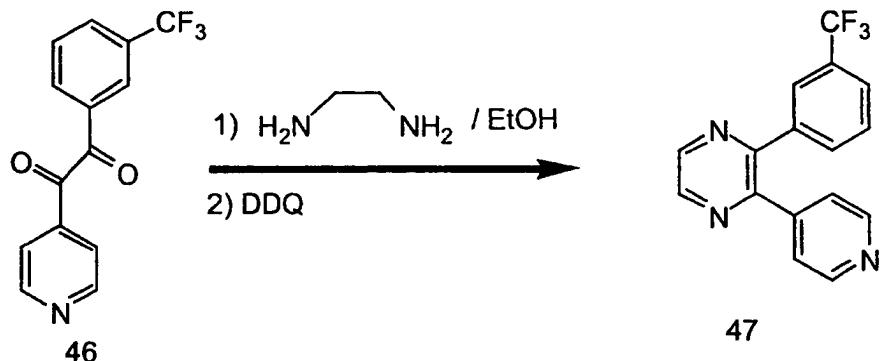


Under Ar, a solution of 45 (7.7 g, 29 mmol) in 5% aqueous dioxane (130 mL) was treated with SeO_2 (12.2 g, 110 mmol) and heated at reflux. After 2h, the reaction was filtered through super-cel and the pad washed with EtOAc. The filtrate was dry packed on silica gel (200 mL) and chromatographed on a Still column (80 mm). The product was eluted with 50% EtOAc-hexanes to yield 2.3 g of 46.

15
20

EXAMPLE 36

2-(pyridine-4-yl)-3-(3-trifluoromethylphenyl)pyrazine (47):



Under Ar, a solution of 46 (2.3 g, 8.2 mmol) in abs.

5 EtOH (100 mL) was treated with ethylene diamine (0.58 g, 9.6 mmol) and heated at 50°C. After 18h, the solution was concentrated to dryness. The residue was partitioned between H₂O and EtOAc (3x) and the organic extracts were dried, filtered and concentrated to dryness. The residue was treated with 10 toluene (125 mL) and DDQ (3.8 g, 16.7 mmol) and then heated to 80°C. After 18h, the reaction was concentrated to dryness. The residue was dry packed with silica gel (100 mL) and chromatographed on a Still column (80 mm). The product was eluted with EtOAc and the common fraction concentrated to dryness. The residue was treated with Et₂O and ethanolic - HCl and concentrated to dryness. The residue was triturated from EtOAc and filtered to yield 100 mg of 47.

Analysis calculated for C₁₆H₁₀F₃N₃ • HCl.

20 C, 56.90; H, 3.28; N, 12.44.
Found: C, 56.45; H, 3.63; N, 12.09

MS (M+1) = 302.1

25 The ability of compounds of the present invention to inhibit the synthesis or the activity of cytokines can be demonstrated using the following *in vitro* assays.

BIOLOGICAL ASSAYS

Lipopolysaccharide mediated production of cytokines

Human peripheral blood mononuclear cells (PBMC) 5 are isolated from fresh human blood according to the procedure of Chin and Kostura, *J. Immunol.* 151, 5574-5585 (1993). Whole blood is collected by sterile venipuncture into 60 mL syringes coated with 1.0 mL of sodium- heparin (Upjohn, 1000 U/ mL) and diluted 1:1 in Hanks Balanced Salt Solution (Gibco). The 10 erythrocytes are separated from the PBMC's by centrifugation on a Ficoll-Hypaque lymphocyte separation media. The PBMC's are washed three times in Hanks Balanced Salt Solution and then resuspended to a final concentration of 2×10^6 cell/ mL in RPMI containing 10% fresh autologous human serum, penicillin 15 streptomycin (10 U/ mL) and 0.05% DMSO. Lipopolysaccharide (Salmonella type Re545; Sigma Chemicals) is added to the cells to a final concentration of 100 ng/ mL. An aliquot (0.1 mL) of the cells is quickly dispensed into each well of a 96 well plate containing 0.1 mL of the test compound, at the appropriate 20 dilution, and are incubated for 24 hours. at 37°C in 5% CO₂. At the end of the culture period, cell culture supernatants are assayed for IL-1b, TNF-a, IL-6 and PGE₂ production using specific ELISA.

IL-1 mediated cytokine production

Human peripheral blood mononuclear cells are isolated from fresh human blood according to the procedure of Chin and Kostura, *J. Immunol.* 151, 5574-5585 (1993). Whole blood is collected by sterile venipuncture into 60 mL syringes coated 30 with 1.0 mL of sodium- heparin (Upjohn, 1000 U/ mL) and diluted 1:1 in Hanks Balanced Salt Solution (Gibco). The erythrocytes are separated from the PBMC's by centrifugation on a Ficoll-Hypaque lymphocyte separation media. The PBMC's are washed three times in Hanks Balanced Salt Solution and then

resuspended to a final concentration of 2×10^6 cell/ mL in RPMI containing 10% fresh autologous human serum, penicillin streptomycin (10 U/ mL) and 0.05% DMSO. Endotoxin free recombinant human IL-1b is then added to a final concentration of 50 pMolar. An aliquot (0.1 mL) of the cells is quickly dispensed into each well of a 96 well plate containing 0.1 mL of the compound at the appropriate dilution. and are incubated for 24 hours. at 37°C in 5% CO₂. At the end of the culture period, cell culture supernatants are assayed for TNF-a, IL-6 and PGE₂

5 synthesis using specific ELISA..

10

Determination of IL-1b , TNF-a, IL-6 and prostanoid production from LPS or IL-1 stimulated PBMC's

15 IL-1b ELISA

Human IL-1b can be detected in cell-culture supernatants or whole blood with the following specific trapping ELISA. Ninety-six well plastic plates (Immulon 4; Dynatech) are coated for 12 hours at 4°C with 1 mg/ mL protein-A affinity chromatography purified mouse anti-human IL-1b monoclonal antibody (purchased as an ascites preparation from LAO Enterprise, Gaithersburg Maryland.) diluted in Dulbecco's phosphate-buffered saline (-MgCl₂, -CaCl₂). The plates are washed with PBS-Tween (Kirkegaard and Perry) then blocked with 1% BSA diluent and blocking solution (Kirkegaard and Perry) for 60 minutes at room temperature followed by washing with PBS Tween. IL-1b standards are prepared from purified recombinant IL-1b produced from *E. coli*.. The highest concentration begins at 10 ng/ mL followed by 11 two-fold serial dilutions. For detection of IL-1b from cell culture supernatants or blood plasma, 10 - 25 mL of supernatant is added to each test well with 75-90 mL of PBS Tween. Samples are incubated at room temperature for 2 hours then washed 6 times with PBS Tween on an automated plate washer (Dennly). Rabbit anti-human IL-1b polyclonal

20

25

30

antisera diluted 1:500 in PBS-Tween is added to the plate and incubated for 1 hour at room temperature followed by six washes with PBS-Tween. Detection of bound rabbit anti-IL-1b IgG is accomplished with Fab' fragments of Goat anti-rabbit IgG-
5 horseradish peroxidase conjugate (Accurate Scientific) diluted 1:10,000 in PBS-Tween. Peroxidase activity was determined using TMB peroxidase substrate kit (Kirkegaard and Perry) with quantitation of color intensity on a 96-well plate Molecular Devices spectrophotometer set to determine absorbance at 450
10 nM. Samples are evaluated using a standard curve of absorbance versus concentration. Four-parameter logistics analysis generally is used to fit data and obtain concentrations of unknown compounds.

15 **TNF-a ELISA**

Immilon 4 (Dynatech) 96-well plastic plates are coated with a 0.5 mg/ mL solution of mouse anti-human TNF-a monoclonal antibody. The secondary antibody is a 1:2500 dilution of a rabbit anti-human TNF-a polyclonal serum purchased from
20 Genzyme. All other operations are identical to those described above for IL-1b. The standards are prepared in PBS-Tween + 10% FBS or HS. Eleven 2 fold dilutions are made beginning at 20 ng/ mL TNF-a.

25 **IL-6 ELISA**

Levels of secreted human IL-6 are also determined by specific trapping ELISA as described previously in Chin and Kostura, *J. Immunol.* 151, 5574-5585 (1993). (Dynatech) ELISA plates are
30 coated with mouse anti-human IL-6 monoclonal antibody diluted to 0.5 mg/ mL in PBS. The secondary antibody, a rabbit anti-human IL-6 polyclonal antiserum, is diluted 1:5000 with PBS-Tween. All other operations are identical to those described above

for IL-1b. The standards are prepared in PBS-Tween + 10% FBS or HS. Eleven 2 fold dilutions are made beginning at 50 ng/ mL IL-6.

PGE₂ production

5 Prostaglandin E2 is detected in cell culture supernatants from LPS or IL-1 stimulated PBMC's using a commercially available enzyme immunoassay . The assay purchased from the Cayman Chemical (Catalogue number 514010) and is run exactly according to the manufacturers instructions.

10

Interleukin8 (IL-8)

The present compounds can also be assayed for IL-8 inhibitory activity as discussed below. Primary human umbilical cord endothelial cells (HUVEC) (Cell Systems, Kirland, Wa) are

5 maintained in culture medium supplemented with 15% fetal bovine serum and 1% CS-HBGF consisting of aFGF and heparin. The cells are then diluted

20-fold before being plated (250 μ l) into gelatin coated 96-well plates. Prior to use, culture medium is replaced with fresh

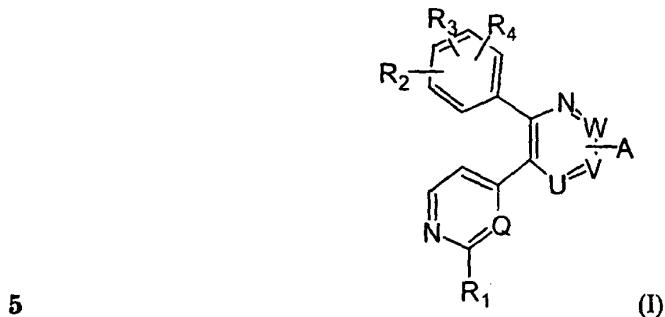
10 medium (200 μ l). Buffer or test compound (25 μ l, at appropriate concentrations) is then added to each well in quadruplicate wells and the plates incubated for 6h in a humidified incubator at 37°C in an atmosphere of 5% CO₂. At the end of the incubation period, supernatant is removed and

15 assayed for IL-8 concentration using an IL-8 ELISA kit obtained from R&D Systems (Minneapolis, MN). All data is presented as mean value (ng/ mL) of multiple samples based on the standard curve. IC₅₀ values

20 where appropriate are generated by non-linear regression analysis.

WHAT IS CLAIMED IS:

1. A compound of the formula

**wherein**

10 A is hydrogen, or a saturated heterocyclic group selected from pyrrolidine, morpholine and piperidine; with the nitrogen atom or atoms optionally substituted with hydrogen or C₁-C₆ alkyl;;

15 Q, U, V and W are independently CH or N;

18 R¹ is hydrogen or NH(C₁-C₆ alkyl) aryl;

20 R², R³ and R⁴ independently represent a member selected from the group consisting of hydrogen, halo, hydroxy, CF₃, NH₂, NO₂, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₁-C₆ alkoxy, substituted C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, substituted C₃-C₈ cycloalkyl, aryl or substituted aryl;

25 or a pharmaceutically acceptable addition salt and/or hydrate thereof, or where applicable, a geometric or optical isomer or racemic mixture thereof.

2. The compound according to Claim 1 wherein

A is hydrogen, or piperidine with the nitrogen atom substituted with hydrogen or C₁-C₆ alkyl;

5

Q, U and W are independently CH or N;

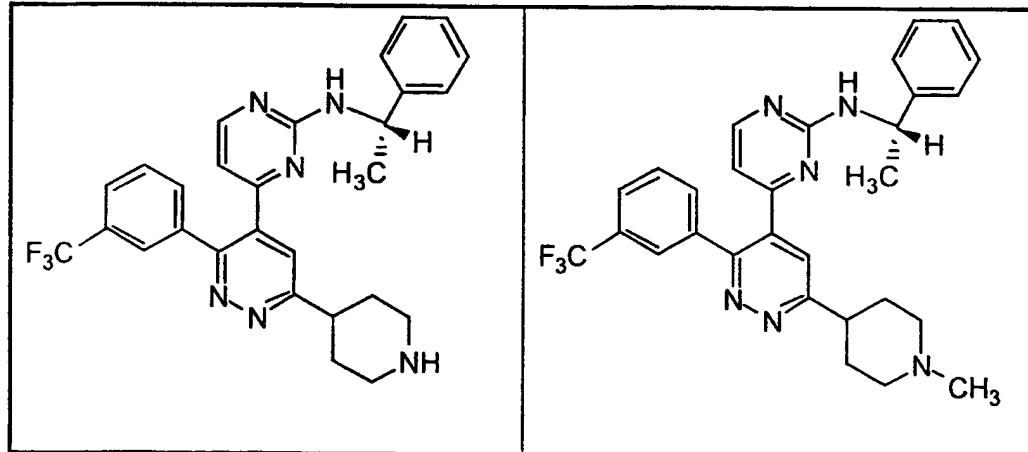
R¹ is hydrogen or NHCH(CH₃) phenyl;

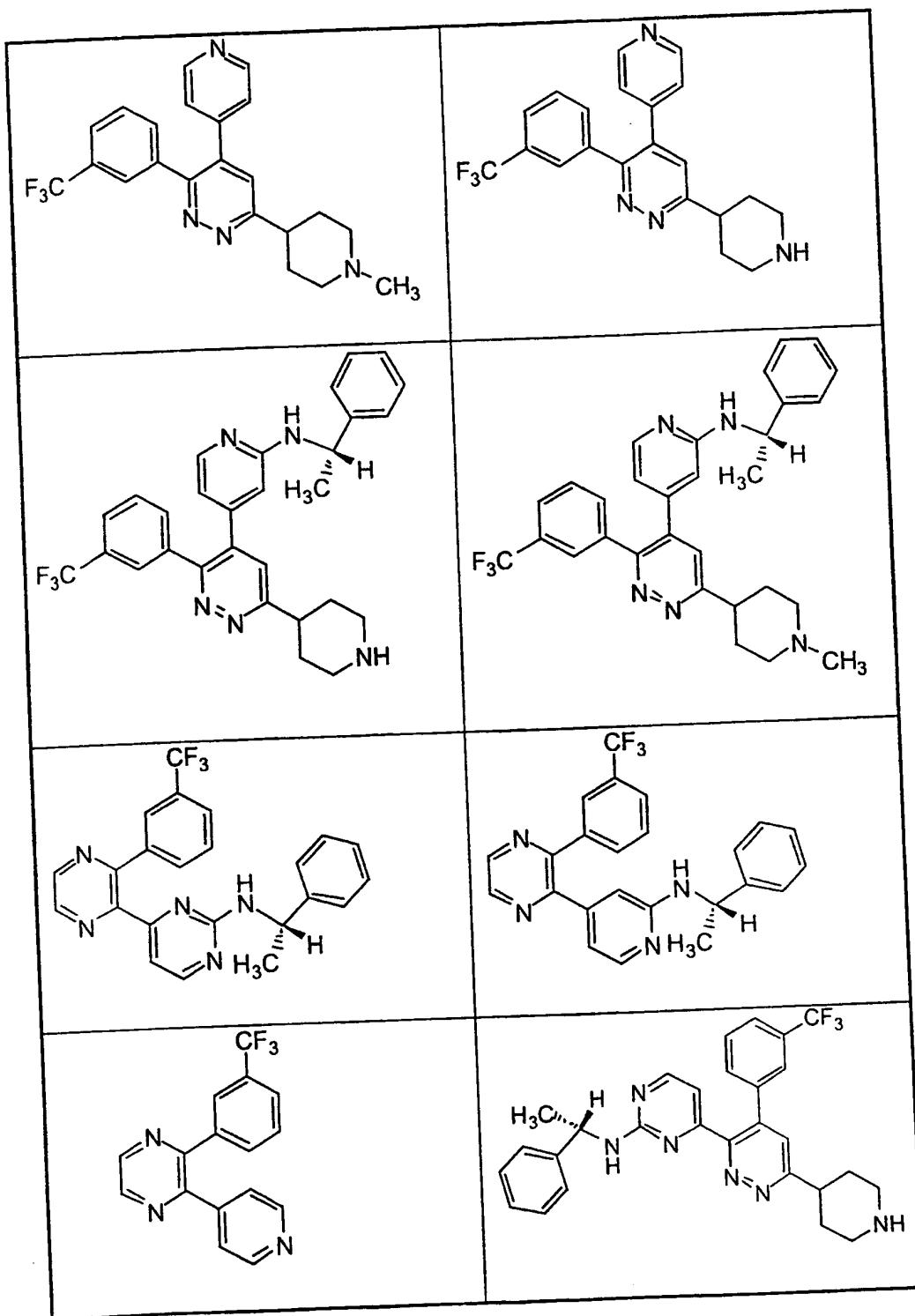
10 R², R³ and R⁴ are independently hydrogen or CF₃;

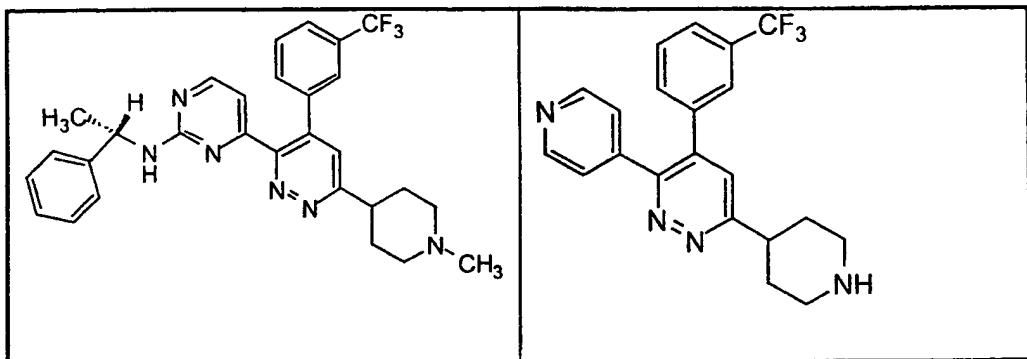
or a pharmaceutically acceptable addition salt and/or hydrate thereof, or where applicable, a geometric or optical isomer or racemic mixture thereof.

15

3. The compound according to Claim 1 represented by one of the following structural formulas:







4. **A pharmaceutical composition which is comprised**

5 **of a compound in accordance with claim 1 in combination with a pharmaceutically acceptable carrier.**

5. **A pharmaceutical composition which is produced**

10 **by combining a compound in accordance with claim 1 and a pharmaceutically acceptable carrier.**

6. **A method of treating a cytokine mediated disease in a mammal, comprising administering to a mammalian patient in need of such treatment an amount of a compound as described in claim 1 in an amount which is effective to treat said cytokine mediated disease.**

7. **A method of treating inflammation in a mammalian patient in need of such treatment, which is comprised of administering to said patient an anti-inflammatory effective amount of a compound as described in claim 1.**

8. **A method in accordance with claim 6 wherein**

25 **the cytokine mediated disease is rheumatoid arthritis, osteoarthritis, endotoxemia, toxic shock syndrome, inflammatory**

bowel disease, tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis or acute synovitis.

5

9. A method in accordance with claim 6 wherein the cytokine mediated disease is rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft v. host rejection, allograft rejection, fever, myalgia due to infection, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis or pyresis.

10. A method of treating osteoporosis in a mammalian patient in need of such treatment, which is comprised of administering to said patient an amount of a compound as described in claim 1 which is effective to treat osteoporosis.

11. A method of treating bone resorption in a mammalian patient in need of such treatment, which is comprised of administering to said patient an amount of a compound as described in claim 1 which is effective to treat bone resorption.

12. A method of treating Crohn's disease in a mammalian patient in need of such treatment which is comprised of administering to said patient an amount of a compound as described in claim 1 which is effective to treat Crohn's disease.

13. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/27184

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) C07D 401/04,401/14,403/04; A61K 31/497, 31/501, 31/506.
US CL 544/238,295,405; 514/252,255.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/238,295,405; 514/252,255.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

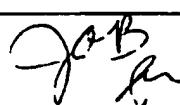
CAS ONLINE STRUCTURE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97/33883 A1 (SMITHKLINE BEECHAM CORPORATION) 18 September 1997, see especially pages 4-9 and example 1 on page 25 and example 3 on page 26.	1-2,4-13
Y	WO 98/24782 A2 (AMGEN INC.) 11 June 1998, see especially page 108, example 1-32 and 1-33 and page 120, example 2-27 as well as remaining pages provided.	1-2,4-13

 Further documents are listed in the continuation of Box C. See patent family annex.

• Special categories of cited documents:	
A	document defining the general state of the art which is not considered to be of particular relevance
E	earlier document published on or after the international filing date
L	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
O	document referring to an oral disclosure, use, exhibition or other means
P	document published prior to the international filing date but later than the priority date claimed
T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
A	document member of the same patent family

Date of the actual completion of the international search 05 FEBRUARY 2000	Date of mailing of the international search report 23 FEB 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer EMILY BERNHARDT Telephone No. (703) 308-1235 

INTERNATIONAL SEARCH REPORT

International application No. PCT/US99/27184

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 1-2 (both in part), 3, 4-13 (all in part)
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

<input type="checkbox"/>
<input type="checkbox"/>

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/27184

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-13 (in part), drawn to compounds,compositions and uses where UVW ring is pyridazine .

Group II, claim(s) 1-13 (in part), drawn to compounds,compositions and uses where UVW ring is pyrazine.

Group III, claim(s) 1-13 (in part), drawn to compounds,compositions and uses where UVW ring is pyrimidine.

Group IV , claim(s)1,2,4-13 (in part), drawn to compounds,compositions and uses where UVW ring is a triazine.

Group V, claim(s) 1,2,4-13 (in part), drawn to compounds, compositions and uses where UVW ring is tetrazine.

Group VI, claim(s) 1,2,4-13 (in part), drawn to compounds,compositions and uses where UVW ring is pyridine.

The inventions listed as Groups I-VI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The groups relate to compounds of considerable structural dissimilarity which are not recognized equivalents of each other. The sole feature common to the groups which does not vary is the presence of a phenyl ring which by itself cannot be considered to define a patentable contribution over the prior art.